

1962 REPORT
of the
SCIENTIFIC DIRECTOR

CLARENCE COOK LITTLE, S.D.

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TOBACCO INDUSTRY RESEARCH COMMITTEE

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Police and Police

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Grants will cover the full cost of the project and, as a condition of award, the grantee must agree to provide a minimum of \$50,000 in matching funds. The maximum grant award is \$500,000. The program is open to all U.S. citizens and permanent residents who are currently employed in the United States. Grants are awarded on a competitive basis and are subject to the availability of funds.

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The Federal Reserve Board will consider the
 policy and program implications of the
 proposed legislation for the Federal Reserve
 System.

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help provide the knowledge and understanding that is necessary for the evaluation of all sorts of studies in connection with the development of a new product. A chapter entitled "How to Write a Chapter on the Development of a New Product" is included in the book.

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TOBACCO INDUSTRY WITH SEARCH FOR COMPLETION
FOLLOWING THE SEARCH FOR COMPLETION

1962 REPORT
of the
SCIENTIFIC DIRECTOR

CLARENCE COOK LITTLE, Sc.D.

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Introduction

During the past year the Tobacco Industry Research Committee has continued and extended its support of research. The major direction continues to be into some of the many clinical and experimental factors that still need to be identified, investigated and evaluated in consideration of the origin of lung cancer, cardiovascular diseases, and other complex constitutional ailments.

While these research studies have increased our factual knowledge, they have at the same time continued to make clear and to emphasize the great and critical gaps in that knowledge. They have confirmed the soundness of the position held and expressed by the T.I.R.C.

This position is that there does not exist the essential experimental and clinical knowledge with which science can even define or identify the multiple factors or influences that may contribute to the origin and progress of these diseases.

This statement holds good as a generalization. It also applies with even greater significance to judgments concerning the causes of these diseases in any individual human being. There have been and will continue to be speculations and opinions on the causes, *but it is a matter of scientific fact that, in our present state of knowledge, no one knows the answers.*

Repetitive Studies Inconclusive

Reported epidemiological findings, resulting from similar surveys that use questionnaires and interviews, indicate certain "associations" between the incidence of these diseases and one or more environmental factors, including tobacco use, especially when that particular factor is singled out for study.

The methodology of such surveys and also the interpretation of their reported findings have been examined and criticized by competent statisticians and epidemiologists.

It is not surprising that every time another survey of this type is conducted under conditions that are broadly similar, the same general results are obtained. However, the *repetition* of an indirect or unsatisfactory scientific procedure does not add to the reliability of the data collected by previous efforts of the same type.

Reviews and reports continue to appear, based mostly on statistically-oriented surveys. The unquestioning, unreserved endorsement, as conclusive, of each such repetitive report, which contains no new or original data but amounts to a statement of opinion, is a disservice to true scientific research. This places an obstacle in the path of accurate recognition and analysis of the problems that remain before us.

As stated, great gaps exist in knowledge of the causes of cancer and of cardiovascular diseases. These result in a large degree from the lack of adequate and controlled methods of bioassay of suspected processes or substances, and from the absence of controlled clinical studies fully utilizing available biochemical tests of metabolic and hormonal changes and developments under different physical, physiological, and mental environments.

Improvement of Research Sought

The T.I.R.C. is continuing its activities in supporting scientific studies and in conducting conferences of scientists in order to delineate methods of improving research in these directions.

As ideas and opportunities for the establishment of new research undertakings are defined, studies will be initiated and continued for whatever period is necessary to solve the many complex problems that universally are recognized as lying ahead.

It is hoped that it may soon be possible for various interested organizations, now conducting or supporting research independently of one another, to cooperate in organizing programs of more sophisticated and potentially more significant studies aimed at filling the gaps in our knowledge.

This should lead to progress more intelligently than does exploiting exclusively any one over-simplified hypothesis of specific environmental causation, or of selective emphasis on any one factor statistically associated with certain causes of death.

No Simple "Magic Bullet" Exists

The need for a broader, more mature and more diversified program of research was evident in results of some investigations reported during 1962.

During that year, scientific work continued to support the view that the quest for a single, simple "magic bullet" to explain the causes or provide the cure for cancer and of heart diseases is unrealistic and probably futile. The interaction of many constitutional and environmental factors and influences, some of which still may be undetected, is becoming increasingly evident.

For this reason alone—the fact that research indicates a possible involvement for these many factors and influences—it is at present scientifically unwise and indeed may be harmful to attribute a simple, definitive, causative role to any one of them, or to attempt to assign them relative degrees of importance.

The smoking of tobacco continues to be one of the subjects requiring study in the lung cancer problem, as do many other agents and influences in modern living. Science does not yet know enough about any suspected factors to judge whether they may operate alone, whether they may operate in conjunction with others, or whether they may affect or be affected by factors of whose existence science is not yet aware. Indeed, it is not known whether these factors actually are "causative" in any real sense.

Research Findings and Studies

During 1962 the Scientific Advisory Board to T.I.R.C. made grants for a number of new projects and awarded grant renewals for continuing work in the broad areas of laboratory experimentation, clinical investigations, and epidemiology. Progress of the research is partly reflected in papers published by recipients of grants. Since the 1961 Report, 60 additional reports have been published, bringing the total to date to 282. Abstracts of the new papers appear elsewhere in this Report, and may be consulted for details on progress of research.

All grants awarded by the Board are for studies that promise to advance the Board's objective of stimulating research that will produce helpful knowledge about what is involved in the problems of lung cancer, coronary disease, and other ailments.

Viruses and Cancer

World-wide scientific interest in the viral theory of carcinogenesis is obvious and growing. Considerable attention was given to this subject at the VIIIth International Cancer Congress held the summer of 1962. Some 50 papers related to the possibility of a viral etiology of cancer were presented, compared with only four papers on that topic at the Cancer Congress held only four years previously. This increased interest in and attention to virus-cancer research is indicative of the rapid changes that can take place in research concepts concerning cancer.

Viruses have been shown to induce a variety of cancers in several animal species. In 1962 there were reports that human adenoviruses known to cause respiratory ailments such as colds, when injected into experimental animals, had resulted in the development of cancers in the animals. As with other agencies, the T.I.R.C.'s research grants in this field have been increasing in recent years.

One T.I.R.C. - supported study is seeking to determine whether injected viral agents, either alone or in combination with various environmental factors, will result in measurable effects on the tracheobronchial tree and pulmonary tissues of laboratory animals. This work also will be extended to include tissues in organ culture.

Another study in progress involves the question of any interrelated role that influenza virus infections, exposure to cigarette smoke and other factors may have in the development of pulmonary and bronchial lesions in mice. This particular study is an extension of work that has been supported for several years into the correlated histology, cytology, and cytochemistry of the tracheobronchial tree and lungs of experimental animals.

Also under way is a project involving the use of chemical agents in virus-free animals to see whether it is possible to elucidate the relationship, if any, between viral and chemical carcinogenesis.

Cell Studies

Of vital importance to virtually all experimental scientific endeavor is work involving the cell. For years the T.I.R.C. has been supporting basic cell research, aiming primarily at the training of more experienced workers and at the development of more reliable and accurate techniques. While previous interest tended to concentrate upon the morphology of cells and morphological changes, the emphasis has now been shifted to the area of the metabolism and behavior of cells in response to various treatments.

Studies now in progress aim at describing basic differences between normal and abnormal, or cancer, cells *in vitro*, regardless of how the cells may be affected by the challenge of some external agent. Of course, in a sense a normal cell in a culture medium is not exactly "normal" because it has been removed from the medium of its natural host.

In one laboratory scientists found that continuous ultraviolet irradiation of the nucleus of a living cell produces damage to the nucleus. Similar damage was found to occur with the use of certain chemical agents.

One important implication of this particular work is the possibility of developing and perfecting a more rapid and accurate bioassay method. A series of agents, among them polycyclic hydrocarbons, are now being tested in the hope of developing a semi-quantitative bioassay for relative carcinogenic potential or activity of a multitude of substances.

On April 21, 1962, the Scientific Advisory Board sponsored a conference on cell differentiation at the Institute for Cancer Research, Philadelphia. Among the topics discussed at the informal session were the factors within cells leading to and guiding differentiation, and the influences on cells of various environmental factors. Chemical reconstitution of undifferentiated to differentiated cells received attention. Discussed were cellular and tissue potentials, influence of chromosomes and genes, various forms of "mutation," organization of tissues, and other topics.

In addition to staff members and members of the SAB, the following were present:

DR. JOHN T. BONNER, Princeton University, Princeton, N. J.
DR. DON W. FAWCETT, Harvard University, Cambridge, Mass.
DR. CLIFFORD W. GURNEY, University of Chicago, Chicago, Ill.
DR. ALFRED E. MIRSKY, Rockefeller Institute, New York.
DR. JOHN RUNNSTROM, Wenner-Gren Institute, Stockholm, Sweden.
DR. F. C. STEWARD, Cornell University, Ithaca, N. Y.

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Cardiovascular Studies

Support of cardiovascular research continues to be an important part of the Advisory Board's research program. This is a complicated and complex field and encompasses, of necessity, a variety of specific topics.

Work continues on a T.I.R.C.-supported project which is seeking to determine if environmental factors have any effect on the development of atherosclerosis as revealed by autopsy studies of accident victims. Trained interviewers are seeking to learn all they can about the victim's life—his diet, his smoking and other habits—to compare or connect this information if possible with the autopsy data.

In the same general field, a T.I.R.C. grantee has reported finding that during smoking there was a rise in serum free fatty acids (FFA) in 17 patients with healed myocardial infarction, aged 36-64. A lesser rise was found during smoking in 16 non-coronary patients, and the researcher suggested that the greater FFA response in the coronary patients resulted from a greater release of catecholamine after nicotine stimulation. This difference in response, if confirmed, may reflect a constitutional difference between persons who are predisposed to coronary disease and those who are not.

It is, of course, not known what the effects may be of repetitive rises in the blood levels of FFA, which actually are a vital body fuel. Post-mortem comparisons of the degree of atherosclerosis in the coronary arteries of smokers and nonsmokers have shown no significant differences. Animal experiments carried out under the T.I.R.C. program have also shown no clear differences in the degree of atherosclerosis in cholesterol-fed animals of several species as a consequence of chronic nicotine irritation.

Smoking and Blood Flow

Of importance in the cardiovascular field is a research project that sought to investigate the effect of tobacco smoking on skeletal muscle

blood flow. There has been conflicting evidence on this subject in the few studies existing in the medical literature.

Working under a T.I.R.C. grant, two Boston investigators used the disappearance rate of a radioactive isotope from skeletal muscle as a measure of its nutritive blood flow. Of 17 normal subjects studied, 14 showed an increase in skeletal muscle nutritive blood flow as measured by the radioisotope disappearance rate during cigarette smoking despite small changes in total calf blood flow and the usual decreases in skin temperature. The mechanism of such an increase still remains unknown. According to the scientists, this work reveals constancy of the increase and suggests that inhalation is not a factor.

The investigators reported that evidently an intact nervous supply to the limb is unnecessary since three of four sympathectomized limbs also showed an increased disappearance rate during smoking. Assuming that skin blood flow does not decrease in sympathectomized limbs during smoking, they said, the increased disappearance rate does not represent a simple shift of blood from the vasoconstricted skin to the muscle.

Nicotine and Carbon Monoxide

The Scientific Advisory Board has also authorized a study to see whether determination of metabolites of nicotine or of carbon monoxide in the blood stream will give more accurate information on the extent to which cigarette users inhale the smoke. Nicotine is absorbed in some degree in the buccal cavity and to a greater degree following deep inhalation of smoke. Carbon monoxide, on the other hand, is reputed to be absorbed only on deep inhalation. Perfection of such methods may permit more accurate determination of true physiological smoke exposure from cigarettes, pipes and cigars than questionnaires on smoking habits and the depth of inhalation, and thus may raise correlation studies to a new level of reliability.

The methods developed in this study will be used by the investigators to help interpret results of another project on the relationship between steroid levels in body fluids and various forms of heart disease and certain types of malignant tumors. This latter project is to be supported by a federal agency.

An investigation has been inaugurated with regard to carbon monoxide. The amounts of carbon monoxide that can be absorbed even through very heavy smoking have been shown to lie well below the toxic level. Since the traces of carbon monoxide present in cigarette smoke are relatively constant, this study will seek to determine whether blood levels of carboxy-hemoglobin, which can be determined very accurately, will reflect the

differences between the amount of smoke contact with the alveoli involved in several different forms of smoking.

Work also is being supported with the objective of learning something about the effects of nicotine on the cerebral circulation. A technique of angiography has been developed whereby it is possible to take what amounts to x-ray "movies" of the blood flow in the cranial vessels including the so-called "circle of Willis," the structural distribution system that monitors regional cerebral arterial flow. This technique has already shown its value in diagnosis of circulatory obstruction.

This and other studies are supplementary to previous indications that nicotine may have stimulating or, in some ways, tranquilizing effects on the central nervous system.

Conference on Cerebral Effects of Nicotine

A conference on the effects of nicotine on the central nervous system was held by the Scientific Advisory Board in New York on Sept. 28, 1962. Work under way in this area and specific topics in need of further research were discussed by grantees and others investigating this particular field. In addition to members of the T.I.R.C. staff and of the Board, the following were present:

- DR. A. K. ARMITAGE, King's College Hospital Medical School, London, England.
- DR. EDWARD F. DOMINO, The University of Michigan Medical School, Ann Arbor.
- DR. ESKIL HANSSON, University of California Medical Center, Los Angeles.
- DR. EBBE CURTIS HOFF AND DR. CHARLES HOCKMAN, Medical College of Virginia, Richmond.
- DR. PAUL S. LARSON, Medical College of Virginia, Richmond.
- DR. EDWARD W. PELIKAN, Boston University School of Medicine.
- DR. H. C. SABELLI, Chicago Medical School, Chicago, Ill.
- DR. CARL C. SELTZER, Harvard University, Cambridge, Mass.
- DR. DUANE G. WENZEL, University of Kansas, Lawrence.

Studies in the Circulatory Area

New studies now being supported in the general circulatory area are concerned with vascular responses to tobacco smoking in patients with vascular disease, the release of catecholamines from the isolated heart, the effect of nicotine and related substance on amine levels in the nervous system, and the influence of drugs on arterial acid mucopolysaccharides.

A study was undertaken to investigate the controversial question whether Buerger's disease and general peripheral vascular disease are separate clinical entities. Research done under a T.I.R.C. grant led the authors to conclude that they are. The study investigated the Buerger syndrome in patients, most of whom were heavy smokers, in the Orient, where it was found to occur with relatively high frequency in Japan and Korea among persons of low socio-economic class, and in the United States.

It was found that those already afflicted with the Buerger syndrome were sensitive to tobacco, but there was no implication that a similar sensitivity occurs in persons with general peripheral vascular disease. Multiple factors of undetermined etiology seem to be involved.

Work in this particular field is continuing with a study of Buerger's disease among various Jewish ethnic groups in Israel. Some scientists have reported that, for some still unknown reason, the disease appears to afflict male Jews more than those of any other race.

Of interest in coronary research are the several studies that have been previously reported on the relationship between the incidence of heart disease and stress. One survey covered 10,000 physicians, dentists, and lawyers subdivided according to the relative stressfulness of their specialties. Its author, a cardiovascular specialist, reported that emotional stress appeared to be an important accelerating factor in atherogenesis when the diet is relatively high in animal fat. Other researchers have reported finding an association between coronary disease and emotional stress and strain. The investigator is about to undertake a similar study with stock market workers under a T.I.R.C. grant.

Smoking and Protein Metabolism

It has long been known that young animals exposed to tobacco smoke or treated chronically with nicotine, gain weight at a lower rate than non-exposed controls. If protein access is adequate, survival of the animals is not impaired.

Following reports from England that rats so exposed excrete more nitrogen than controls during the duration of the exposure, an investigation was begun to determine whether an analagous effect can be observed in healthy, young human subjects.

Genetic and Psycho-Physiological Factors

Of continuing interest to the Scientific Advisory Board and to others is the relatively unexplored problems of the varying and differing characteristics of people—genetic, psychological and physiological—and the bearing of such differences on disease predisposition.

It is now recognized from a number of studies here and abroad that there are measurable or detectable differences both among people who smoke in various ways and between those who do and those who do not smoke, suggesting that smoking practices may in part reflect constitutional factors that may influence different disease predilections.

One study of male patients at chest clinics reported that the personality traits of lung cancer patients differed significantly from those of cancer-free persons.

A T.I.R.C.-supported study of a biologically and culturally homogeneous group of Italian-American factory workers, almost all born in this country, found that the leaner individuals smoke significantly more than the stout or fat, but not muscular, ones. Contrary to other previous reports, the smokers in this group were no less masculine in physique, no more active, and consumed no more alcohol than nonsmokers.

Another continuing study is seeking to determine or define the precursors of hypertension and coronary artery disease in a group of medical school students. Reports already have indicated that a familial factor is involved. A prospective phase of this long-term project is the analysis of figure drawings obtained from the students. It is believed that these figure drawings may provide a simple, effective, psychological screening device for the personality appraisal of normal subjects.

Also continuing is a study of the psychological, cultural and health characteristics of aging smokers and nonsmokers. Another investigation just beginning will seek to examine the extent of and constitutional basis for differences in taste sensitivities, and their possible correlation with any constitutional predisposition to pathologic conditions, with differences in smoking practices and with food dislikes. Also getting under way is a study into psychological influences upon the translation of motives into action with smoking behavior as an instance.

Chemistry and Biochemistry

The Scientific Advisory Board awarded a grant to scientists at North Carolina State College to measure the levels of arsenic absorption by tobacco plants in relation to soil content of the element and to estimate the residual levels of arsenic in the soils used for tobacco growing in various parts of the state.

The study found that arsenic in soils ranged from 1 to 5 parts per million (ppm), with an average for all areas of the state of 2.8 ppm. This value is close to the 4 ppm reported by J. E. Greaves in 1913 for a virgin soil and thus suggests that there has been no measurable increase from the previous use of arsenical insecticides in the arsenic contents of soil in which tobacco is grown.

The investigators reported arsenic in the cured leaf of tobacco grown in these soils was from 0.5 to 3.55 ppm, with an average for all leaf samples of 1.5 ppm.

Also under T.I.R.C. support is a study designed to see whether various amounts of trace metals, including arsenic and nickel, when added to tobacco, will have any effect on the incidence of pulmonary adenomas in Strain A mice that inhale the smoke from such tobacco. Control studies will administer the same metals by other routes.

Another supported project will attempt to identify individual polyphenolic compounds in cigarette smoke and to estimate their amounts. Where feasible, these compounds will be prepared for future or concurrent studies on their metabolism and possible effect on human beings.

Epidemiological Area

A study is now under way into the influence of certain environmental factors in the genesis of neoplastic disease in tuberculosis patients and in children. The work is being done by four California scientists who received a grant from T.I.R.C. to augment their current project of testing the hypothesis that medical uses of radiation are associated with an increase in the incidence of leukemia or other malignancies.

The T.I.R.C.-supported project will seek to study the incidence of lung cancer or other cancer in tuberculosis patients with a design that would ascertain the relationship, if any, between lung cancer in such patients and three factors—tuberculosis, smoking habits, and radiation exposure.

Also under way in Massachusetts is an epidemiological lung cancer study designed to check a previous investigation. The investigators found in earlier work that there appeared to be a statistical correlation between lung cancer and cigarette smoking, respiratory illness, heavy consumption of alcohol, and outdoor occupation. They said that while the statistical correlation between lung cancer and cigarette smoking was strongest, the data suggested that a threshold in consumption had to be passed before a linear relationship occurred. The data further showed, they reported, that the same level of cigarette use with *addition* of pipe or cigar smoking diminished the disease association, a result difficult to interpret.

Lung Physiology

Certain phases of the actual mechanical work of the human lung remain a mystery to science. One such phase is pulmonary clearance—exactly how does the lung remove inhaled particles. A study now under way in this subject deals with the phagocytes found in the pulmonary alveoli.

The work began with the concept of measuring the overall lung clearance capacity of healthy, intact rabbits. Radioactive silver iodide, I-131, (which is also used by meteorologists to seed clouds for production of rain) was introduced into the lungs of the rabbits by a non-inhalation procedure. The movement of the radioactive element was then traced with sensitive measuring equipment. It was found that eventually all of the I-131 was engulfed by the alveolar phagocytes and carried to the alimentary canal whence it was excreted.

The current phase of the study encompasses the inhalation of whole cigarette smoke following introduction of the I-131 in order to determine the overall effect on clearance rates and the relative rates by alternative routes. Other animals are to be used in the project in addition to the rabbit, and drugs that affect the flow of mucous also are to be investigated, as well as the effects of other inhaled gases and aerosols.

Alveoli Studied in Pulmonary Emphysema

Recent discovery that a powerful surfactant substance lines the alveoli has gone far toward explaining the hitherto mysterious physical characteristics of these structures and their behavior during expansion and contraction. Moreover, the effects of this agent and the consequences of its deficiency suggest that a biochemical approach to the investigation of the etiology of emphysema may now be within reach.

A project has been sponsored in which lung tissues obtained at surgery and at autopsy are being studied. It will attempt to measure the relative activity of this surfactant recovered from lungs afflicted with carcinoma, emphysema, and bronchiectasis. Effort will be made to determine whether tobacco smoke inhalation affects the activity of this surfactant, and further study of its chemistry will be undertaken.

A report by a T.I.R.C. grantee in 1962 said that bronchial disturbances may produce an obstructive airway mechanism leading to air trapping as well as indirectly influence surface tension phenomena in the lung or impair clearance of entrapped pollutants. In this way, the report said, erosion of the alveolar membrane is initiated.

Other Projects

Among the other projects, which are under way in institutions throughout the country, are:

A study of the nasal and pharyngeal bacterial flora of smokers, non-smokers and former smokers.

The classification, prognosis and possible etiologic factors in primary lung tumors as determined from postmortem observations.

A comparative study of the effects of 3-methylcholanthrene and cigarette smoke condensate applied to the oral tissues of Swiss mice in which liver damage has been previously induced.

The purification and structure determination of the chlorogenic acid isomers.

Mechanisms of the psychotropic effects of nicotine.

Fellowship Program

In 1962, as in every previous year since 1955, the T.I.R.C., upon recommendation of the SAB, provided funds for the granting of fellowships to the nation's accredited medical and osteopathic schools. Nearly 600 young men and women have so far received fellowships.

Deans of the schools choose the fellows, and the students, working with their faculty advisors, determine the subjects they wish to study during summer or other off-term time. The fellowship program seeks to stimulate interest in basic research among medical school students and any subject of study may be selected by fellows, without regard to its relevance to tobacco use or effects.

Summary

This narrative section seeks only to indicate briefly some of the more recent findings and trends. More complete details will be found in previous Annual Reports and in the abstracts they contain. Work in many of these fields is continuing to receive support.

In closing, it seems appropriate to reiterate the basic belief underlying the Advisory Board's position, which was fully expressed in the Board's report two years ago. That report concluded with this paragraph:

"As the tobacco industry continues its support of the search for truth and knowledge, it must recognize, as is always the case in true scientific research, there can be no promise of a quick answer. The important thing is to keep on adding to knowledge until the accumulative facts provide the basis for a sound conclusion."

Abstracts of Reports

Each recipient of a Tobacco Industry Research Committee grant-in-aid is responsible for the initial presentation or publication of the results of his research in scientific meetings or in appropriate scientific journals.

Following are abstracts, approved by the authors, of research reports acknowledging support from the T.I.R.C. that have appeared in scientific journals since the 1961 Report of the Scientific Director.

These abstracts have been grouped under the following headings: I. Studies at the Cellular Level; II. Pulmonary Physiology and Anatomy; III. Cardiovascular Studies; IV. Psycho-Physiological Studies; V. Tobacco Chemistry and Biochemistry; VI. Pharmacology; VII. Other Studies; VIII. Review.

I. Studies at the Cellular Level

"INDUCTION OF CHANGES IN SURFACE ACTIVITY OF STRAIN L CELLS AT GAS-MEMBRANE INTERFACES." By Philip Cooper, Irene Goldring and Morris Klein. Departments of Surgery, Albert Einstein College of Medicine and Bronx Veterans Administration Hospital, New York, N. Y. *Science*, March 2, 1962, pages 725-726. (T.I.R.C. grantee: Cooper)

During an investigation of the effects of various gaseous agents on the growth of strain L and HeLa cells in cell culture, the immediate direct effect of the passage of particulate and non-particulate gases over the surface of these cells, in a Rose perfusion chamber, was observed. The gaseous agents included smoke from the combustion of cigarettes, of cigarette tobacco only, of cigarette paper, and of onionskin paper, and non-smoke gases such as carbon monoxide, hydrogen sulfide, illuminating gas, oxygen, and helium.

Immediately after the injection of all gases tested there is a very rapid increase of the surface area of the cell as well as increased granularity. Most evident, however, is "blebbing" of the surface of the cells, which is most marked near the center of the bubbles of gas and is not seen on the surfaces of neighboring cells.

The "blebbing" persists as long as bubbles of gas remain in the perfusion chamber. If the contaminated medium is replaced by fresh medium within 10 to 15 minutes after contamination, the cells are promptly restored to their original appearance. If "blebbing" is allowed to continue for more extended periods, cellular activity gradually decreases and the cells die. "Blebbing" does not occur when cells in a chamber without medium are exposed to air or medium alone, under various degrees of increased pressure.

It appears that the "blebbing" results from a disturbance of the sol-gel relationship of the cell surfaces and apparently can occur at a gas-membrane interface.

"ALTERATIONS IN GROWTH OF STRAIN L CELLS EXPOSED TO SMOKE GASES." By Philip Cooper, Morris Klein and Irene P. Goldring, Albert Einstein College of Medicine and Bronx Veterans Administration Hospital, New York, N. Y. *Proceedings of the Society for Experimental Biology and Medicine*, Volume 110, pages 11-13, May 1962.

The present series of studies was undertaken to elucidate further the direct action of smoke on living cells maintained in a culture medium. The test substances included smoke from the combustion of cigarettes, cigarette tobacco, cigarette paper, onionskin paper, and tobacco-wrapped cigarettes. Smoke was collected under sterile conditions. The culture flasks were inverted and the prescribed volume of smoke was introduced into each flask. The flasks were re-inverted, the fluid medium was allowed to wash over the cells, and the flasks were gently agitated until all smoke was absorbed by the medium.

Control cultures were treated in exactly the same manner, except that they received similar doses of sterile air. The effect of non-smoke gases, including illuminating gas and carbon monoxide, was studied under similar conditions.

Under the conditions of this study it appears that there is a "toxic" effect of smoke gases on strain L cells in culture. This results both in morphological changes in the cells and in alterations in growth curves, as indicated by the reduction of cell populations. The smoke from the combustion of either cigarette paper or onionskin paper appeared to be more "toxic" than that from the combustion of whole cigarettes or cigarette tobacco alone. Smoke from paper contained more particulate matter than smoke from cigarette tobacco or the whole cigarette, suggesting that the particular matter present in smoke gases may be of significance.

"CULTIVATION OF NORMAL AND MALIGNANT HUMAN LUNG TISSUE. I. THE ESTABLISHMENT OF THREE ADENOCARCINOMA CELL STRAINS." By Mary V. Reed, Ph.D., and George O. Gey, M.D., Finney-Howell Cancer Research Laboratory, Department of Surgery, Johns Hopkins Hospital, Baltimore, Md. *Laboratory Investigation*, Vol. 11, pages 638-652, August 1962. (T.I.R.C. grantee: Gey)

The ultimate goal of these studies is the establishment of autologous strains of normal and malignant lung epithelium for subsequent comparative studies with each other and with embryonic lung cells in regard to cytologic and biochemical characteristics and responses to viruses.

Specimens from 41 human cases provisionally diagnosed as lung carcinomas and from 11 human embryonic lungs were cultured in roller tubes on collagen, in plasma clot, and on the glass surface with different concentrations of unsupplemented human serum and of serum fortified with synthetic media. Normal bronchial epithelium gave early responses with beating cilia surviving 2 to 3 months.

Human carcinoma cells from the lung possess metabolic advantages over their normal prototypes as determined by their preferential survival and growth in continuous culture. Stromal dominance may mitigate against such responses and often accounts for failures to obtain either normal or malignant cell growth in continuous culture.

The three human tumorous epithelial cell strains described in this paper are in the second, fourth and fifth years respectively. Two were established from poorly differentiated adenocarcinomas of the lung, and one was a metastatic carcinoma of the breast to the lung. Each strain has distinctly different cytologic and growth characteristics.

Other grantors: American Cancer Society and National Cancer Institute.

"EFFECTS OF SELECTIVE ULTRAVIOLET IRRADIATION OF THE NUCLEI OF LIVING CELLS." By P. O'B. Montgomery, F. Van Orden, L. L. Hundley, C. L. Chapman and J. E. Cook, Department of Pathology, University of Texas Southwestern Medical School, Dallas. *Proceedings of the Society for Experimental Biology and Medicine*, Volume 108, pages 372-375, November 1961. (T.I.R.C. grantee: Montgomery)

Continuous ultraviolet irradiation of the nucleus of a living cell produces nuclear damage. Although this damage resembles nuclear damage which occurs when the entire cell is irradiated, it is less severe due to the protection of the cytoplasm from the effects of irradiation. Continuous ultraviolet irradiation of the nucleus of a living cell produces cytoplasmic damage resembling that which occurs when the entire cell is irradiated, but is less pronounced.

"EFFECTS OF ACETONE AND PHENOL ON ESTABLISHED CELL LINES CULTIVATED *IN VITRO*." By Donald M. Pace and Alice Elliott, Institute for Cellular Research, Department of Physiology, University of Nebraska, Lincoln. *Cancer Research*, Vol. 22, pages 107-112, January 1962. (T.I.R.C. grantee: Pace)

Acetone and phenol, which are common constituents of cigarette smoke, have been studied in various concentrations with reference to their short-term effects on mouse fibroblast and human skin cells cultivated *in vitro*.

Concentrations of acetone, 10.0 mg/ml and above, are toxic to both types of cells. The skin cells are more sensitive to acetone effects than are the fibroblast cells. Although 5.0 mg/ml acetone is not toxic to fibroblasts within a 10-day period, it is noticeably so to the skin cells.

Phenol in concentrations of 0.2 mg/ml and above is very toxic and kills the cells within an hour or two. In concentrations of 0.1 and 0.16 mg/ml some of the fibroblast cells were still living after 10 days, but a definite inhibitory effect was indicated: only 15% of the cells survived for that period. The skin cells appeared to be less sensitive: 57% of the cells survived 10 days after exposure to 0.16 mg/ml of phenol concentrate.

Other grantor: The Cooper Foundation, through the University of Nebraska Foundation.

"THE EFFECTS OF SULPHUR DIOXIDE UPON ESTABLISHED CELL LINES CULTIVATED *IN VITRO*." By James R. Thompson and Donald M. Pace, Institute for Cellular Research, University of Nebraska, Lincoln. *Canadian Journal of Biochemistry and Physiology*, Volume 40, pages 207-218, February 1962.

Gaseous sulphur dioxide has been cited as one of the major contaminants of the air, yet very little is known about its mode of action upon living tissue other than as a "respiratory irritant." The feasibility of utilizing tissue culture methods for long-term studies of the effects of low concentrations of air pollutants upon cells was demonstrated by the exposure to SO_2 and its salts of cultures of Strain L mouse cells (fibroblasts), mouse liver cells, and HeLa cells derived from an epithelial carcinoma of the human cervix.

The HeLa cells were more sensitive to SO_2 exposure than the mouse cells, which seems to support the general thesis that humans are more sensitive to sulphur dioxide than other mammals.

Cells cultivated in biological medium grow in concentrations of gaseous SO_2 up to 2000 p.p.m., although somewhat inhibited. Cells subjected to a concentration of 500 p.p.m. in this medium are not greatly affected and their growth is comparable to those cells in control cultures. The addition of various salts of SO_2 in concentrations from 10 to 200 mg % produced responses ranging from complete inhibition of growth (by 200 mg % NaHSO_3) to apparent stimulation of growth by some concentrations of Na_2SO_4 .

"INFLUENCE OF NICOTINE ON CELLS OF RABBITS' AORTA AND MYOCARDIUM IN TISSUE CULTURES." By Tatsuo Kokubu and O. J. Pollak, Dover Medical Research Center, Dover, Del. *Experimental and Molecular Pathology*, Volume 1, pages 293-303, June 1962. (T.I.R.C. grantee: Pollak)

The association of cigarette smoking with cardiovascular diseases in several statistical studies prompted study of the effect of cigarette smoke condensate and tobacco constituents on cardiovascular cells *in vitro*.

This paper concerns the effect of nicotine added to nutrient media before inoculation or after growth of aortic and myocardial cells from normo- and hypercholesteremic rabbits. The concentrations of nicotine used were arrived at by trial and error. Solutions weaker than 1:40,000 added to the nutrient before inoculation were ineffective; solutions of greater concentration than 1:1,000 proved too strong; other tests were at concentrations of 1:2,500, 1:5,000 and 1:10,000.

Addition of nicotine to the nutrient before inoculation inhibited cell growth, resulting in fewer positive cultures, and there was severe and often fatal damage to the structure of various cells. Inhibition of cell growth reflected by the number of positive cultures, depression of cell proliferation and multiplication, damage to cell structure, and the speed and degree of recovery from damage all mirrored the concentration of nicotine applied. Character and extent of morphologic damage as well as recovery from same depended also on the cell type. Length of cell exposure to nicotine was a strong factor in recovery of cells.

Other grantor: National Heart Institute.

"MORPHOLOGICAL AND CYTOLOGICAL STUDY OF HUMAN AMNION CELLS IN THE COURSE OF RECOVERY FROM RADIATION INJURY." By Masahiro Mizutani, Yuh H. Nakanishi and C. M. Pomerat, University of Texas Medical Branch, Galveston. *Texas Reports on Biology and Medicine*, Vol. 19, pages 811-824, Winter 1961. (T.I.R.C. grantee: Pomerat)

A well-established human amnion strain which was cultivated in Rose chambers was irradiated with 1000r from a cobalt⁶⁰ source. The materials thus treated were stained with Jacobson's method daily for five successive days following irradiation. The changes in cell population and mitotic index and the incidence of giant and multinucleate cells were examined. A population of this strain which had a modal chromosome number of 75 showed severe injury after irradiation. The cell cultures grown from the recovery

of radiated cell cultures were characterized by a modal chromosome number of 73. The mechanism of giant cell formation and the changes in the modal chromosome numbers have been discussed in reference to reported evidence.

Other grantor: School of Aviation Medicine, USAF, Randolph Air Force Base, Texas.

II. Pulmonary Physiology and Anatomy

"PROTECTIVE EFFECT OF PARASYMPATHETICOMIMETIC AGENTS ON CILIATED MUCUS-SECRETING EPITHELIUM." By Hans L. Falk, Ph.D., Paul Kotin, M.D. and Herta M. Tremmer, Ph.D., Departments of Pathology, University of Southern California School of Medicine and Los Angeles County General Hospital. *Journal of the National Cancer Institute*, Volume 27, pages 1379-1392, December 1961. (T.I.R.C. grantee: Falk)

Exposure of ciliated mucus-secreting epithelium of the esophagus of the frog to parasympatheticomimetic agents protects against the effects of irritant aerosols so that the slowing of mucous stream induced by the latter does not occur. The agents studied include 1) acetylcholine and choline-like drugs, 2) cholinesterase inhibitors, and 3) compounds related to nicotinic acid. Prior application of such parasympatheticomimetic agents exerts a prophylactic effect against the subsequent action of irritants.

Irritants present in the particulate phase of cigarette smoke and urban polluted air induce a slowing in the rate of flow in the mucous stream, probably as a result of alterations of ciliary activity and modification of mucous secretion. *In vivo* this has been shown to facilitate prolonged retention of particulate matter settling on the respiratory epithelium of mice, rats, and rabbits. When the particulates consist of or contain known carcinogenic agents, their possible role in the pathogenesis of pulmonary cancer is suggested.

Despite the demonstration of carcinogenic agents in polluted urban air and cigarette smoke, analysis of epidemiological data reveals that by far the greater majority of those exposed to this carcinogenic milieu do not develop pulmonary cancer.

To us an attractive and plausible explanation for this epidemiological pattern is that local and systemic host factors are significantly concerned with the entry and action of carcinogenic agents.

Other grantors: National Cancer Institute and American Cancer Society. **"PANLOBULAR EMPHYSEMA: ANATOMY AND PATHODYNAMICS."** By John P. Wyatt, M.D., Vernon W. Fischer, and Herbert C. Sweet, M.D., FCCP, Departments of Pathology and Medicine, St. Louis University School of Medicine, St. Louis, Mo. *Diseases of the Chest*, Vol. 41, pages 239-259, March 1962. (T.I.R.C. grantee: Wyatt)

Panlobular emphysema is a morphologic denominator common to such unlike conditions as primary humpback chest deformities, localized hardening of the hilus of the lung, or large bronchial airways deformities and congenital "lobar" emphysema. Less well-defined is the airway obstruction in chronic bronchitis and bronchiectasis observed in many cases of established panlobular emphysema. An additional emphysematous group without struc-

tural bronchial deformity was also found, but these were usually associated with lesser degrees of emphysema.

Bronchial disturbances may produce not only an obstructive airway mechanism leading to air trapping, but indirectly influence surface tension phenomena within the lung or impair clearance of entrapped pollutants and in this way initiate erosion of the air sac membranes.

Hypertrophy of the right ventricle was a frequent companion of established cases of generalized panlobular emphysema. The air-to-blood exchanging surface — the pulmonary contribution to homeostasis — is progressively destroyed through alveolar sac dissolution with the concurrent loss of the perfusing lung bed being responsible for the common clinical manifestations of cor pulmonale.

Other determinants involved in the development of cor pulmonale are pathologic by-passes from artery to vein, bronchopulmonary shunting particularly in emphysema with fibrosis and a decompensating portal azygos-pulmonary vein system. These morphological findings reflect the primary importance of the pulmonary-cardiac disease in the natural history of this form of emphysema.

III. Cardiovascular Studies

"THE VIBROCARDIOGRAPHIC EXERCISE TEST FOR CORONARY INSUFFICIENCY." By Clarence M. Agress, M.D., FACC, and Stanley Wegner, Cardiovascular Research Laboratory, University of California, Department of Medicine, Los Angeles, California; *American Journal of Cardiology*, Vol. 9, pages 541-546, April 1962. (T.I.R.C. grantee: Agress)

The data obtained from this study represent a small group of patients and, therefore, can only be considered as a preliminary report. Since the patients selected were a carefully-studied group, however, greater accuracy can be expected than from mass data collection. The vibrocardiographic exercise test performed is a quantitative test dependent on a numerical measurement only, and is free of qualitative interpretation.

Initial deflections of the vibrocardiogram were measured before and after a single two-step test in 81 patients, including both normals and persons with myocardial ischemia. The normal response was a widening of the wave intervals, expressed as a ratio of total systole, the increase ranging from 5 to 200%. In abnormal subjects there was a decrease ranging from 5 to 63%.

Normal and functionally normal patients correlated with their clinical diagnoses in 87% of the cases by the two-step test and 94% by the vibrocardiographic interval test. In abnormal patients the correlations were 66% and 88% respectively.

An additional 85 cases including both single and double two-step tests have been added to the study with no essential change in the above conclusions.

"EFFECT OF NICOTINE ON THE CORONARY BLOOD FLOW AND RELATED CIRCULATORY PARAMETERS. CORRELATIVE STUDY IN NORMAL DOGS AND DOGS WITH CORONARY INSUFFICIENCY." and "EFFECTS OF PERSANTIN (RA.), A NEW CORONARY

VASODILATOR. ON CORONARY BLOOD FLOW AND CARDIAC DYNAMICS IN THE DOG." By Samuel Bellet, M.D., James W. West, Ph.D., Otto F. Muller, M.D. and Ugo C. Manzoli, M.D., Division of Cardiology, Philadelphia General Hospital and Department of Pharmacology and Robinette Foundation, University of Pennsylvania Medical School, Philadelphia. *Circulation Research*, Vol. 10, pages 27-34 and 35-44, January 1962. (T.I.R.C. grantee: Bellet)

The effect of intravenously administered nicotine (20 micrograms/Kg/min) on coronary blood flow and related hemodynamic parameters was studied in the normal intact dog and in the dog with induced chronic coronary insufficiency. Nicotine increased cardiac work markedly in both groups of dogs by an increase in the mean arterial blood pressure and cardiac output.

Mean control coronary blood flow was moderately decreased in dogs with coronary artery ligation and markedly decreased in dogs with narrowing of the two main branches of the left coronary artery. Increase in coronary blood flow produced by nicotine in normal dogs was observed to be as high as 125% on an average over the control value. The average increase was 82.5% with ligation of one coronary artery branch and 83.3% with narrowing of the two main branches.

The response of the coronary flow was directly related to the degree of coronary narrowing and/or occlusion; the greater the impairment, the smaller was the increment in coronary blood flow, which frequently dropped below the control value in the post-infusion period. Coronary vascular resistance and myocardial oxygen utilization declined during nicotine administration.

Persantin, a new coronary vasodilator, produced an average increase in coronary blood flow of 159% over control values in normal animals, of 165% in dogs with ligation of one coronary artery branch, and of 51% in dogs with coronary artery narrowing without increasing cardiac contractility or cardiac work.

Other grantors: The Eli Lilly Company, the Life Insurance Medical Research Fund, and the American Heart Association.

"EFFECT OF CIGARETTE SMOKING ON FREE FATTY ACIDS IN PATIENTS WITH HEALED MYOCARDIAL INFARCTION." By Alfred Kershbaum, M.D., Samuel Bellet, M.D., FACC, Raymond F. Caplan, M.D., and Leonard J. Feinberg, Ph.D., Philadelphia General Hospital, Pennsylvania. *American Journal of Cardiology*, Volume 10, pages 204-208, August, 1962.

The effect of smoking on serum free fatty acids (FFA) was studied in 17 patients with healed myocardial infarction, aged 36-64, including one female. There was an average maximal rise of 65.6% in FFA in all subjects in 10 to 20 minutes after smoking two cigarettes in a 10 minute period. Some elevation usually persisted for 40 minutes.

In 16 non-coronary patients FFA elevations after smoking averaged 27.2%, and in 10 normal subjects the average maximal rise was 24.6%. In 13 non-smoking controls, there was an average maximal rise of 1.7% during the test period.

It is suggested that the greater FFA response in myocardial infarction patients is the result of a greater catecholamine release after nicotine stimulation.

Other grantor: National Heart Institute.

"METABOLIC, HISTOLOGIC AND HISTOCHEMICAL ASPECTS OF THE HOMOGRAFTED HEART." By R. J. Bing and (by invitation) C. Chiba, A. Chrysohou, S. Gudbjarnason, and P. L. Wolf, Wayne State University College of Medicine, Detroit, Mich. *Transactions of the Association of American Physicians*, Volume 74, pages 318-332, 1961. (T.I.R.C. grantee: Bing)

Metabolic studies on the homografted canine heart demonstrated in some preparations high respiratory quotients existing together with increased pyruvate, negative myocardial ketone extractions, and diminished pH in coronary vein blood. The percentage glucose oxygen extraction ratios frequently exceeded 100%. These changes suggested glycolysis, with a breakdown of pyruvate through the fatty acid rather than the tricarboxylic acid cycle. The respiratory chain, however, appeared to be intact, since differences in oxidation reduction potentials between coronary arterial and vein blood were negative. Apparently, homograft rejection resulted in increased cell permeability with loss of enzymes and coenzymes from the cell.

The two basic pathologic processes present in the sections of the homografted hearts were granulomatous myocarditis similar to the acute proliferative stage of rheumatic fever but lacking fibrinoid necrosis and myocardial necrosis after 8 days of viability. This pattern is most likely due to an immune tissue response. Histochemical studies demonstrate active production of RNA protein in the graft and marked reduction in malic dehydrogenase in the donor heart after grafting.

"TRANSPLANTATION OF THE HEART." By Richard J. Bing, Chiyo Chiba, Athanasios Chrysohou, Paul L. Wolf and Sigmundur Gudbjarnason, Department of Medicine, Wayne State University College of Medicine and Harper Hospital, Detroit, Mich. Editorial, in *Circulation*, Volume 25, pages 273-276, February 1962.

Transplantation immunity, resulting in the rejection of the homograft, is the result of antigens from the graft, which, on reaching the regional lymph nodes, stimulate production of lymphoid cells which infiltrate the graft and destroy it. Transplantation immunity may be actively acquired, and adaptive immunity to the homograft also has been demonstrated. Although the nature of the antigens is not known, it has been shown that cells can be morphologically disintegrated without destroying their power to elicit transplantation immunity, and it has been demonstrated that the antigenic substances are especially concentrated in the nuclear fraction of disintegrated cells.

In this laboratory, two dissimilar pathologic processes were observed in homografted canine hearts: one lesion consisted of a diffuse pancarditis (granulomatous infiltration) that was strikingly similar to the proliferative stage of acute rheumatic fever. The second type of change observed was acute myocardial necrosis with interstitial edema and polymorphonuclear neutrophilic infiltration of the fragmented myocardial tissue. It is not likely that homografts of the heart will be of any clinical importance in the foreseen future. However, it is probable that some fundamental knowledge can be

gained from a careful study of the correlation between the progression of homograft reaction and the metabolism of the transplanted heart.

"THE RELATIONSHIP BETWEEN CORONARY BLOOD FLOW, MYOCARDIAL OXYGEN CONSUMPTION AND CARDIAC WORK AS INFLUENCED BY PERSANTIN." By Vernon E. Wendt, M.D., John F. Sundermeyer, M.D., Pancras B. den Bakker, M.D. and Richard J. Bing, M.D., FACC, Department of Medicine, Wayne State University College of Medicine and Harper Hospital, Detroit, Mich. *American Journal of Cardiology*, Volume 9, pages 449-454, March 1962.

The effect of a pyrimido-pyrimidine derivative, Persantin, on coronary blood flow, myocardial oxygen consumption and cardiac work was studied in nine patients without cardiovascular disease. Persantin caused a decrease in coronary vascular resistance. The dissociation between cardiac work and myocardial oxygen consumption suggests that Persantin acts upon cellular metabolism, causing an increase in the oxygen demands and necessitating an increase in coronary blood flow. The administration of Persantin resulted in a decline in the ratio of left ventricular work to myocardial oxygen consumption. It is concluded that the drug, like nitroglycerin, diminishes cardiac work in some patients and has a direct effect on cardiac metabolism.

"CATECHOLAMINES IN HOMOLOGOUS HEART GRAFTS." By A. Wegmann, C. Chiba, A. Chrysohou and R. J. Bing, Department of Medicine, Wayne State University College of Medicine, Detroit, Mich. *Proceedings of the Society for Experimental Biology and Medicine*, Volume 109, pages 543-545, March 1962.

Complete denervation of puppy hearts was accomplished by homologous transplantation. Cardiac content and intracellular distribution of catecholamines remained unaffected the first 24 hours following transplantation. Within this time period accelerated rejection did not influence the catecholamine content of the heart graft. After 72 hours no catecholamines could be detected in transplanted heart.

"STUDIES ON THE TRANSPLANTED HEART. ITS METABOLISM AND HISTOLOGY." By C. Chiba, M.D., P. L. Wolf, M.D., S. Gudbjarnason, Ph.D., A. Chrysohou, M.D., H. Ramos, M.D., B. Pearson, M.D., and R. J. Bing, M.D., Departments of Medicine and Pathology, Wayne State University College of Medicine, and Harper Hospital, Detroit, Mich. *Journal of Experimental Medicine*, Volume 115, pages 853-866, April 1962.

The metabolic changes in the homografted canine heart were studied in order to define the biochemical alterations accompanying homograft rejection. The homografted heart released pyruvate and lactate as well as malic dehydrogenase and aldolase. Extraction of glucose by the graft usually remained positive.

In several experiments, homograft rejection was accelerated by prior sensitization of the host animal. During the accelerated rejection, the release of pyruvate and lactate was more pronounced, and even glucose appeared in increased concentrations in coronary vein blood.

In many experiments the respiratory quotient of the transplanted heart as well as its glucose-oxygen extraction ratio were elevated. It seems likely

that the elevated respiratory quotients were the result of the conversion of carbohydrates to fat. The metabolic block or blocks present in the transplanted heart are likely to be the result of diminution of intracellular enzymes and coenzymes resulting from increased cellular permeability.

Other grantors: U.S. Public Health Service, American Heart Association, Michigan Heart Association, Life Insurance Medical Research Fund, Burroughs-Wellcome Fund, and John A. Hartford Foundation.

"MYOCARDIAL METABOLISM IN A PATIENT WITH HASHIMOTO'S THYROIDITIS AND HYPOTHYROIDISM." By P. B. den Bakker, M.D., J. F. Sundermeyer, M.D., V. E. Wendt, M.D., M. Salhaney, M.D., S. Gudbjarnason, Ph.D., and R. J. Bing, M.D. *American Journal of Medicine*, Volume 32, pages 822-826, May 1962.

A case of Hashimoto's thyroiditis with hypothyroidism is presented. Cardiac output, coronary blood flow and myocardial oxygen consumption were within the normal range. Pyruvate and lactate were extracted by the heart during the basal state and released by the heart on exercise. A marked increase in myocardial glucose:oxygen extraction ratio was found and the differences in oxidation-reduction potential between arterial and coronary vein blood were positive at rest and exercise. The results suggest glycolysis in the cardiac muscle of this individual in the presence of normal myocardial oxygen usage.

"THE REDOX-POTENTIAL OF THE LACTATE-PYRUVATE SYSTEM IN BLOOD AS AN INDICATOR OF THE FUNCTIONAL STATE OF CELLULAR OXIDATION." By Sigmundur Gudbjarnason and Richard J. Bing. *Biochimica et Biophysica Acta*, Volume 60, pages 158-162, June 1962.

The redox-potentials of heart muscle, arterial and coronary-vein blood have been calculated from the ratio of lactate/pyruvate in the presence and absence of myocardial anoxia. In absence of myocardial anoxia, the redox-potential of heart muscle is more positive than that of arterial blood; the redox-potential of coronary-vein blood approaches that of the heart muscle. In myocardial anoxia the redox-potential of heart muscle is more negative than that of arterial blood; that of coronary-sinus blood approaches that of the muscle. The results of this study suggest that alterations in ΔE_h across the heart reflect parallel changes in the myocardium.

"FREE FATTY ACID CONCENTRATION AND COMPOSITION IN ARTERIAL BLOOD." By Martin E. Rothlin, Christine B. Rothlin and Vernon E. Wendt, Department of Medicine, Wayne State University College of Medicine, Detroit, Mich. *American Journal of Physiology*, Vol. 203, pages 306-310, August 1962. (T.I.R.C. grantee: Bing)

The effect of the administration of norepinephrine, glucose and insulin, pentobarbital, and Hypertensin on the arterial concentration and composition of plasma free fatty acids (FFA) has been studied in man and dog. With a rise of the FFA concentration as produced by norepinephrine, the contribution of oleic acid to the total FFA increased, while that of stearic and palmitic acids decreased. The reverse changes in the FFA composition were observed when their arterial level fell under the influence of other agents studied. The FFA composition was dependent on the FFA concentra-

tion in arterial blood, but not on the experimental condition of the subject or animal at the time of analysis. At high FFA levels, the FFA composition approached that of depot fat.

"THE ROLE OF THE HEART IN SHOCK." By Richard J. Bing, M.D., and Herminio Ramos, M.D. *Journal of the American Medical Association*, pages 871-873, September 8, 1962.

These studies have indicated that oxygen lack leads to rapid dephosphorylation of higher energy phosphate compounds and to the subsequent formation of inorganic phosphorus. In the heart completely deprived of oxygen, glycogen also disappears rapidly. Alterations in the carbohydrate intermediates during myocardial anoxia are also well defined. The manifold and diverse disturbances in intermediary metabolism produced by anoxia could well lead to depression of myocardial contractility in shock. It is also quite possible that the deterioration of myocardial expulsive power contributes to the development of irreversible circulatory failure.

"OXIDATION REDUCTION IN HEART MUSCLE. THEORETICAL AND CLINICAL CONSIDERATIONS." By S. Gudbjarnason, Ph.D., R. O. Hayden, M.D., V. E. Wendt, M.D., T. B. Stock, M.D. and R. J. Bing, M.D., Department of Medicine, Wayne State University College of Medicine, Detroit, Mich. *Circulation*, Volume 26, pages 937-945, November 1962.

The purpose of this report is to point out that changes in the oxygen-reduction (redox) potential of a certain redox system in the blood perfusing the heart muscle reflect alterations within heart muscle cells. A review of clinical and experimental findings by these authors and others illustrates the limited value of calculations of the state of cellular oxidation in heart muscle from a comparison of the redox potential in arterial and coronary vein blood. Efforts should be made to accomplish this goal by more specific and refined biochemical means. Incorporation of labeled precursors into substrates present in coronary vein blood may prove a useful subject for study.

"CATECHOLAMINE CONTENT OF VARIOUS ORGANS IN EXPERIMENTAL HYPERTENSION." By A. Wegmann, K. Kako, and R. J. Bing, Wayne State University College of Medicine, Detroit, Mich. *American Journal of Physiology*, Vol. 203, pages 607-608, October 1962.

Nephrogenic hypertension in dogs produced by a unilaterally placed Goldblatt clamp resulted in diminished catecholamine content in the thoracic aorta, both kidneys, and in the spleen. The catecholamine content in heart, brain, and the adrenal glands remained unaffected. Neurogenic hypertension, induced by partial section of buffer nerves, had no significant effect on the catecholamine content of these organs.

"TOTAL CALF AND MUSCLE NUTRITIVE BLOOD FLOW DURING TOBACCO SMOKING." By Jay D. Coffman, M.D. and Stanley L. Javett, M.D., Massachusetts Memorial Hospitals, Boston, Mass. *Proceedings of the New England Cardiovascular Society*, Volume 20, pages 37-39, 1961-62. (T.I.R.C. grantee: Coffman)

There is conflicting evidence in the few studies available in the medical literature concerning the effect of tobacco smoking on skeletal muscle blood

flow. In the use of a plethysmograph alone it is apparent that increases in muscle blood flow may be hidden or exaggerated by changes in skin blood flow; therefore, the effect of tobacco smoking has been investigated by using the disappearance rate of a radioactive isotope from skeletal muscle as a measure of its nutritive blood flow.

Of a group of 17 normal subjects, 14 showed an increase in skeletal muscle nutritive blood flow as measured by the radioisotope disappearance rate during cigarette smoking despite small changes in total calf blood flow and the usual decreases in skin temperature. The mechanism of such an increase is the unanswered question. These studies reveal its constancy and suggest that inhalation is not a factor.

Evidently an intact nervous supply to the limb is not necessary since 3 of the 4 sympathectomized limbs showed an increased disappearance rate during smoking. Assuming that skin blood flow does not decrease in sympathectomized limbs during cigarette smoking, it is not a simple shift of blood from the vasoconstricted skin to the muscle.

"NORMAL ROENTGENOGRAPHIC ANATOMY OF THE HUMAN CIRCLE OF WILLIS." By Robert A. Kuhn, M.D., Department of Neurosurgery, New York Medical College, New York City. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, Vol. 86, pages 1040-1049, December 1961.

In preparation for a study of the effects of tobacco on the cerebral circulation, it was important to establish the normal vascular pattern of the human circle of Willis, the structural distribution system which monitors regional cerebral arterial flow. Development of a technique of retrograde cerebral angiography to determine the flow patterns was accomplished, involving the use of a 50% hypaque solution. The technique avoids completely pressure artifacts and arterial injury.

Clear visualization is obtained of components of the circle of Willis by this method. The observations indicate that the human circle of Willis is functionally a circle in name only. The independent anterior and posterior segments possess major differences in function. Internal carotid flow normally supplies the ipsilateral half of the anterior segment, but about 50% of individuals possess the capacity to maintain adequate functional circulatory flow to both hemispheres of the brain by way of one internal carotid artery.

Posterior segment circulation is characterized by bilateral distribution of a relatively small volume of slowly moving arterial blood. The brain stem and cerebellar areas are, therefore, usually isolated from the rapidly moving high volume stream perfusing the anterior segment. In the usual individual, if the internal carotid supply fails bilaterally there would appear to be little chance that hemispherical perfusion could be supported by way of posterior segment flow.

"THE SPEED OF CEREBRAL CIRCULATION." By Robert A. Kuhn, M.D., New York Medical College, Flower and Fifth Avenue Hospitals, New York City. *New England Journal of Medicine*, pages 689-695 October 4, 1962.

In order to establish a normal rate of cerebral blood circulation, tests were conducted in six adults and one child by retrograde brachial injection below the right axilla and by high-speed angiography, thus providing an opportunity for study of brain circulation in a physiologic setting.

The average thorax-to-thorax circulation time in the adult is seven seconds. Cerebral transit usually is accomplished within four seconds. The velocity of blood flow is quite high through the anterior segment of the circles of Willis and through the anterior and middle cerebral arteries. Brain-stem and posterior cerebral irrigation, by contrast, is sluggish. Reasons for these differences are as yet unclear.

Flow rates in children are more rapid than those in the adult. Total cervical-cerebral circuit may be completed in as little as five or six seconds. Hemodynamic factors are believed to be responsible for these higher velocities. The capillary phase in adult and child is equal in duration — approximately two seconds.

"ACTION OF NICOTINE ON CORONARY VASCULAR RESISTANCE IN DOGS." By Lloyd E. Leaders and J. P. Long, Department of Pharmacology, State University of Iowa College of Medicine, Iowa City. *American Journal of Physiology*, Volume 203, pages 621-625, October 1962. (T.I.R.C. grantee: Long)

Nicotine administered intra-arterially in adult mongrel dogs produced an increase in coronary vascular resistance as indicated by an increase in coronary perfusion pressure. It was concluded that this results from sympathetic nervous system activity or release of catecholamines from chromaffin tissue. Ganglia or ganglion-like structures are apparently involved.

The contractile force of the myocardium, as well as coronary perfusion pressure, was increased with intra-coronary administration of nicotine or norepinephrine and sympathetic nerve stimulation. Coronary vascular resistance was increased by these agents and procedures. This increase may or may not be related to the positive inotropic effects of nicotine.

The ultimate effect of intra-arterial administration of nicotine, contrary to some previous reports, is an increase in coronary resistance which would be expected to result in a decrease in coronary blood flow.

Other grantor: U.S. Public Health Service.

"THE BUERGER SYNDROME IN THE ORIENT." By Victor A. McKusick and Willard S. Harris. Department of Medicine, the Johns Hopkins University School of Medicine and Hospital. *Bulletin of the Johns Hopkins Hospital*, Vol. 109, pages 241-291, December 1961. (T.I.R.C. grantee: McKusick)

1. The Buerger syndrome — occlusive peripheral vascular disease with the clinical picture described by Buerger — occurs in relatively high frequency in Japan and Korea and probably in other parts of the Orient. It affects almost exclusively males. Onset is before 35 years of age in a majority of cases. The patients are almost without exception smokers, usually heavy smokers. The upper extremities as well as the lower extremities are affected in a significant proportion of cases. Thrombophlebitis occurs in some cases.

Auscultation was found useful in identifying involvement of the iliac and femoral arteries. A frequent arteriographic finding in cases with involve-

ment of the arms was persistence and dilatation of the interosseous artery with occlusion of the radial and/or ulnar arteries. Occasionally a pulse in a perforating branch of the interosseous artery was palpable at the wrist and communications from the interosseous artery to the ulnar artery were identified arteriographically in some. In the legs a comparable finding — a perforating branch of the peroneal artery communicating with the terminal portion of the anterior tibial artery — was observed. The deep femoral artery was occluded in two patients.

2. In Korea and Japan the Buerger syndrome occurs predominantly in farmers and laborers, persons of lowest socioeconomic status.

3. Other impressive epidemiologic features are exposure and trauma, and a low level of dietary fat and protein consumption.

4. In a series of twenty-eight cases two patients had occlusive disease in the iliac arteries with symptoms starting at the age of 33 and 35 years and possibly secondary to trauma to the low back and sacrum. These two cases appear to represent a condition distinct from the others.

5. In a majority of the cases atherosclerosis, embolism and occlusive disease in the aorta and iliacs cannot account for the process. Most of the cases studied appear to represent a distinct category of vascular disease which can legitimately be termed Buerger's disease.

6. Histopathologic study of amputated specimens from nine Korean males revealed nonspecific organizing and recanalizing occlusion in eight. In one changes consistent with subacute angiitis were observed.

7. Multiple factors in the series of cases and perhaps even in individual cases may be responsible for the initiation and perpetuation of a process which is, within limits, progressive.

Other grantors: U.S. Public Health Service and the Eizai Company, Japan. "THE BUERGER SYNDROME IN THE UNITED STATES. ARTERIOGRAPHIC OBSERVATIONS. WITH SPECIAL REFERENCE TO INVOLVEMENT OF THE UPPER EXTREMITIES AND THE DIFFERENTIATION FROM ATHEROSCLEROSIS AND EMBOLISM." By Victor McKusick, Willard S. Harris, Ole E. Ottesen and Richard M. Goodman, Departments of Medicine and Radiology, The Johns Hopkins University School of Medicine and Hospital, Baltimore, Md. *Bulletin of the Johns Hopkins Hospital*, Volume 110, pages 145-176, March 1962.

Aortograms, femoral arteriograms, and brachial arteriograms were performed in twelve male patients with clinically typical Buerger syndrome. The average age of onset was 27 years (range 15 to 43). All were heavy smokers, and in most, remission and relapse were intimately related to cessation and resumption of smoking.

Superficial phlebitis had occurred in at least five (Nos. 1, 5, 6, 7 and 10); histologic material supporting the diagnosis of Buerger's disease was present in at least four (Nos. 1, 3, 4 and 6) and will be described elsewhere. No evidence of occlusive disease of the aorta and its large branches supplying the extremities was discovered. No evidence of atherosclerosis of noteworthy proportions was discovered.

These and other arteriographic findings were strikingly similar to those in Korean patients with the Buerger syndrome (McKusick et al., *Bull. Johns Hopkins Hosp.* 109:242, 1961). It is concluded that the arteriographic features are sufficiently characteristic to represent one more argument that Buerger's disease exists as an entity distinct from other forms of arterial disease. Whether the disorder is of essentially inflammatory nature, that is, an angiitis, is a problem for histologic study.

Other grantor: National Institutes of Health.

"BUERGER'S DISEASE: A DISTINCT CLINICAL AND PATHOLOGIC ENTITY." By Victor A. McKusick, M.D., Willard S. Harris, M.D., Ole E. Ottesen, M.D., Richard M. Goodman, M.D., William M. Shelley, M.D., and Robert D. Bloodwell, M.D., Johns Hopkins Hospital and School of Medicine, Baltimore, Md. *Journal of the American Medical Association*, pages 5-12, July 7, 1962.

Arteriographic and histopathologic study of a group of 22 patients in Baltimore provided evidence that Buerger's disease is a distinct clinical and pathologic entity. Precocious atherosclerosis and systemic embolism can be excluded as diagnostic possibilities. Although the changes in the vessels are inflammatory in character, it may not follow that they represent an angiitis comparable to panarteritis. The etiologic factors and the pathogenetic mechanisms in Buerger's disease are ill understood.

In Korea and Japan, where Buerger's disease is relatively more common than in the United States, exposure to damp cold and possibly to trauma seemed to be initiating factors in the young male subjects studied, nearly all of whom lived in farm villages and worked long hours in rice paddies with hands and feet in cold water. In both the oriental and Baltimore cases, cigarette smoking seemed to be a potent exacerbating and perpetuating factor in the disease.

Other grantor: National Institutes of Health.

"CORONARY VASOMOTOR TONUS IN ATHEROSCLEROTIC DOGS." By Cecil E. Cross and Robert W. Oblath, Department of Medical Research, St. Joseph Hospital, Burbank, California. *American Journal of Physiology*, Volume 202, pages 616-618, April 1962. (T.I.R.C. grantee: Dr. P. F. Salisbury, of St. Joseph Hospital)

An atherogenic regimen imposed upon dogs resulted in several distinct abnormalities of the coronary circulation. The structure of the coronary arteries was modified by extensive atheromatous deposits. During control states before the administration of vasoactive drugs, coronary flow per unit of net propulsive force and heart weight was unvaried or increased. The ability of the atheromatous coronary tree to increase or decrease its vasomotor tonus was markedly curtailed. The abnormalities recorded were proportional with the severity of the atherogenic regimen.

"LOCAL CIRCULATION IN HEART MUSCLE STUDIED WITH Na²⁴ CLEARANCE METHOD." By Peter F. Salisbury, Cecil E. Cross, Robert W. Oblath, and P. Andre Rieben, Department of Medical Research, St. Joseph Hospital, Burbank, California. *Journal of Applied Physiology*, Volume 17, pages 475-478, May 1962. (T.I.R.C. grantee: Salisbury)

The disappearance of radioactivity of Na^{24}Cl , injected into the left ventricular walls of dogs, was studied. The rate of Na clearance from individual deposits did not measure coronary flow in absolute terms; however, when, in the course of a single observation, the Na clearance slope changed, this reflected directional variations of coronary flow. Increased central coronary pressure did not always result in more rapid sodium clearance from ischemic regions of heart muscle.

"VENTRICULAR PERFORMANCE MODIFIED BY ELASTIC PROPERTIES OF OUTFLOW SYSTEM." By Peter F. Salisbury, M.D., Ph.D., Cecil E. Cross, and P. Andre Rieben, B.S. *Circulation Research*, Volume 11, pages 319-328, August 1962.

Left ventricular and atrial pressures, left ventricular circumference and longitudinal meridional segment length, coronary flow, and cardiac oxygen consumption were measured in dogs under conditions which permitted intentional variation of the elasticity of the left ventricular outflow system, and comparison of cardiac performance during steady states in which heart rate, stroke work, and stroke volume were identical but the outflow elastic storage capacity was varied.

When ejecting through a rigid system, the left ventricle generated a larger fraction of the contractile tension under auxotonic conditions, and left ventricular systolic peak pressure was increased. Ejections through rigid tubes proceeded from higher diastolic ventricular pressures and larger external dimensions. The effort of hearts which ejected through rigid outflow conduits was associated with a reduced myocardial oxygen consumption.

Other grantor: National Heart Institute.

"CORONARY VASOMOTOR TONUS IN MODERATE HYPOTHERMIA." By Cecil E. Cross, P. Andre Rieben and Peter F. Salisbury, Department of Medical Research, St. Joseph Hospital, Burbank, California. *American Journal of Physiology*, Volume 203, pages 825-828, November 1962.

Coronary blood flow was measured in mongrel dogs in open-chest preparations with fixed cardiac output and by-passed right heart. Arterial oxygen tension (pO_2), pH, and temperature were measured. The slope of regression lines between mean coronary driving pressure (aortic pressure minus left ventricular pressure) and coronary flow indicated directional changes of coronary vasomotor tonus.

During periods of blood cooling in non-failing hearts, the coronary vessels dilated only when pO_2 was permitted to fall, but not when it remained stable. In failing hearts, moderate decreases of blood temperature and pO_2 did not cause further decrements of coronary vasomotor tonus. The data indicate that diminished pO_2 and not low blood temperature was the factor that caused coronary vasodilation.

IV. Psycho-Physiological Studies

"CONSTITUTION AND SMOKING IN ITALIAN-AMERICAN FACTORY WORKERS." By Albert Damon, Department of Epidemiology, Harvard School of Public Health, Boston, Mass. *American Journal of*

Physical Anthropology, Volume 20, pages 67-68, March 1962.

Because of inconsistent and infrequent reports of association of tobacco smoking with body form, it was desirable to study as homogeneous a group — biologically and culturally — as possible, in this case 167 adult males, aged 20-59, working in a single factory, all with parents born within 75 miles of Naples, Italy; 151 were born in the United States.

Among these 167 men, the leaner individuals smoked significantly more than the stout or fat (but not muscular) ones. The biserial coefficients of correlation were higher when non-smokers and light smokers were compared with heavy smokers than when non-smokers were compared with all smokers. The associations, though significant, were not particularly close, or close enough for individual prediction, with biserial coefficients from 0.25 to 0.35.

The association was not due to different diets, since smoking and caloric intake, total as well as percentages of protein, carbohydrate, total fat, saturated fatty acids, and polyunsaturated fatty acids were not associated. As reported by previous authors, serum cholesterol levels were significantly higher in the smokers. Contrary to previous reports, the smokers were no less masculine in physique, no more active, and consumed no more alcohol than non-smokers.

"STUDIES ON FIGURE DRAWINGS: A REVIEW OF THE LITERATURE (1949-1959)." By Leona W. Jones, Ph.D., and Caroline B. Thomas, M.D., Johns Hopkins University School of Medicine, Baltimore, Maryland. *The Psychiatric Quarterly Supplement* Vol. 35, pages 212-261, Part II, 1961. (T.I.R.C. grantee: Thomas)

As part of a long-term study of precursors of hypertension and coronary artery disease, figure drawings have been obtained from 779 Johns Hopkins medical students in twelve successive classes. The present paper is a review of the figure-drawing literature for the purpose of providing a broad background for a projected series of studies in regard to figure drawings, their scoring classification and their use in the appraisal of personality in a population of healthy medical students on whom a wide variety of other data are available. In forthcoming articles, comparisons will be made between the figure drawings of smokers and nonsmokers, of subjects with and without a parental history of hypertension and/or coronary artery disease, with and without hypercholesteremia, and with different types of body build.

The review of the figure-drawing literature from 1949 through 1959 indicates an expanding interest in the use of the Draw-A-Person test, with increasing emphasis on its role as a research tool. As yet there is no universally accepted scoring procedure, although many investigators have devised their own scoring classification. At least one major study has demonstrated that reliable scoring can be achieved and that statistically significant correlations can be made between scores for drawings and other tests scores such as those of the Rorschach test. Accordingly, the authors believe that the Draw-A-Person test offers promise of becoming a simple, effective, psychological screening device for the personality appraisal of normal subjects.

"COMPARISON OF SMOKERS AND NON-SMOKERS. II. THE DIS-

TRIBUTION OF ABO and Rh(D) BLOOD GROUPS." By Bernice Hirschhorn Cohen, Johns Hopkins University School of Hygiene and Public Health, and Caroline Bedell Thomas, Johns Hopkins University School of Medicine, Baltimore, Md. *Bulletin of the Johns Hopkins Hospital*, Vol. 110, pages 1-7, January 1962.

The distributions of the ABO and Rh blood groups among 1398 healthy white and Negro men classified according to smoking habits were examined. No significant differences were found in any of the comparisons among the Negro males. Among the white males, there appeared to be a significant deficiency of group B individuals among heavy cigarette smokers and an excess of group B persons among non-smokers and occasional smokers. An excess of Rh negative individuals was found in the white occasional smoker group. The differences, while not marked, seem sufficient to warrant further investigation of the relationship between smoking habits and blood groups, along with other pertinent variables.

Other grantor: U. S. Public Health Service.

"PSYCHOLOGICAL, CULTURAL, AND HEALTH CHARACTERISTICS OF AGING SMOKERS AND NON-SMOKERS." By Frederick E. Whiskin, M.D., Andrew S. Dibner, Ph.D., and Paul J. Rhudick, Ph.D., the Age Center of New England, Inc., Boston, Mass. *Journal of Gerontology*, Volume 17, pages 69-74, January 1962. (T.I.R.C. grantee: Whiskin)

Demographic, health, psychological, and cultural characteristics of 402 aged smokers and non-smokers were examined with questionnaire techniques. There were 153 male smokers and 21 male non-smokers and 126 female smokers and 102 female non-smokers in the study group.

None of the hypotheses pertaining to health attitudes or psychological factors was substantiated. However, such dimensions as inhaling and attitude toward smoking among smokers seemed to be related to certain psychological and health attitudes as well as to onset and cessation of the habit.

Most men started smoking before they were 25 years old (80%), while only 35% of the women had started by then; 42% of the men but only 29% of the women reported they inhaled; 52% of the men and 37% of the women felt more relaxed while smoking; 10% of the men and 6% of the women felt smoking was beneficial, and 29% of the men and 22% of the women thought it harmful.

Only about 15% of each group said they wanted to cut down their smoking, and only one-third of the men and women believed they could definitely stop smoking if they so desired.

The dimensions of inhaling versus non-inhaling tended to separate the smokers into two groups which showed statistically significant differences with respect to the following characteristics: inhalers are more concerned about their health, tend to believe that smoking is harmful to them, are not certain that they could stop smoking, feel less relaxed while smoking, smoke more non-filter cigarettes, smoke more of the cigarette, and started smoking at an earlier age, as compared to the non-inhalers.

Among smokers and non-smokers, cultural factors were of importance, particularly in relation to parental attitude. Smokers of both sexes had fathers who smoke more often than was the case with non-smokers. Women

smokers more frequently indicated parental restrictions on smoking than women who did not smoke.

An interesting observation which is difficult to evaluate is that most smokers did not report being influenced by the publicized findings of a relationship between smoking and cancer. This attitude seems contradictory, because some of the respondents who so responded nonetheless admitted concern over health. This finding may be influenced by the fact that older people in general exhibit more health concern but do not necessarily relate it to their smoking habits.

V. Tobacco Chemistry and Biochemistry

"AFFINITY OF POLYCYCLIC AROMATIC HYDROCARBONS FOR ELECTRONS WITH THERMAL ENERGIES: ITS POSSIBLE SIGNIFICANCE IN CARCINOGENESIS." By Prof. J. E. Lovelock, National Institute for Medical Research, London, England, and Prof. A. Zlatkis and Prof. R. S. Becker, Department of Chemistry, University of Houston, Texas. *Nature*, February 10, 1962, pages 540-541. (T.I.R.C. grantee: Becker)

In previous studies (Lovelock, 1960-61) it was found that most classes of hydrocarbon had little or no affinity for free electrons with thermal energies, although there were several exceptions to this rule. This paper reports some preliminary observations on the electron affinity of tetracyclic aromatic hydrocarbons, and discusses the possible relationship between electron affinity and carcinogenic activity with these and other compounds.

The results of the experiments indicate that among hydrocarbons the class of polycyclic aromatic compounds is unusual in possessing many members with a high affinity for free electrons. So far, most experimental work and theoretical considerations of the electron distribution in these compounds has been concerned with their undoubted ability to function as electron donors. This fact has tended to overshadow the essentially ambivalent character of the polycyclic hydrocarbons in electron transfer reactions.

It was suggested in the previous studies that the toxicity or biological activity of compounds with high electron affinity was attributable to their ability to function as irreversible electron traps, so that the normal transfer of electrons during oxidative phosphorylation was impaired. The possibility that carcinogenic activity is a special example of this form of toxic action is supported by recent experimental work (Allison, A. C. & Lightbown, J. W., *Nature* 189:892, 1961).

The notion that an ability to extract electrons from their normal path in a living cell is a necessary molecular property of a major class of chemical carcinogens is speculative, but is relatively accessible to experimental verification or denial.

"POTENTIAL METHOD FOR THE DETERMINATION OF ELECTRON AFFINITIES OF MOLECULES: APPLICATION TO SOME AROMATIC HYDROCARBONS." By W. E. Wentworth and Ralph S. Becker, Department of Chemistry, University of Houston, Texas. *Journal of the American Chemical Society*, Vol. 84, pages 4263-4266, Nov. 20, 1962.

One of the principal aims of this investigation is to establish the fundamental nature of the electron capture by molecules occurring in a detector used in gas chromatography. The interpretation is developed in terms of an equilibrium between the neutral molecules and the electrons. The relationship between the electron capture coefficients and the electron affinities of molecules is presented. The results for a series of aromatic hydrocarbons are compared to the half wave reduction potentials. If certain assumptions are made concerning the ratio of the partition functions of the gaseous negative ion of the molecule to the neutral gaseous molecule, the electron affinity of the molecule can be estimated. This has been carried out for anthracene and other aromatic hydrocarbons, and the results compare favorably with recent theoretically calculated values.

"STUDIES ON THE BIOSYNTHESIS OF THE PYRIDINE RING OF NICOTINE." By Thomas Griffith, Kenneth P. Hellman, and Richard U. Byerrum, Department of Biochemistry, Michigan State University, East Lansing. *Biochemistry*, Volume 1, pages 336-340, March 1962. (T.I.R.C. grantee: Byerrum)

Tobacco plants were fed three C^{14} -labeled substrates to study their role in the biosynthesis of the pyridine ring of nicotine. Glycerol-2- C^{14} and aspartic acid-3- C^{14} both contributed relatively large quantities of radioactive carbon to the pyridine ring, whereas propionate-3- C^{14} did not. Glycerol-2- C^{14} was incorporated into the pyridine ring to about the same extent as glycerol-1,3- C^{14} .

Partial degradation of the pyridine ring of nicotine from plants fed aspartic acid-3- C^{14} revealed that aspartic acid was not converted directly to the ring, since C^{14} was located in more than a single position in the ring. The three labeled compounds all contributed C^{14} to the pyrrolidine ring of nicotine. The pattern of labeling in the pyrrolidine ring suggested that propionate was converted to acetate before utilization for nicotine biosynthesis.

"SYNTHESIS OF PYRROLIDINE RING OF NICOTINE FROM SEVERAL C^{14} -LABELED METABOLITES OF *NICOTIANA RUSTICA*." By Pei-Hsing Lin Wu, Thomas Griffith, and Richard C. Byerrum, Kedzie Chemical Laboratory, Michigan State University, East Lansing. *Journal of Biological Chemistry*, Volume 237, pages 887-890, March 1962.

Acetate, propionate, glycerol, and aspartate were utilized by *Nicotiana rustica* for synthesis of the pyrrolidine ring of nicotine. When acetate-1- C^{14} was metabolized by the plants over a 7-day period, 95% of the C^{14} incorporated into nicotine was located in the pyrrolidine ring and this was equally divided between positions 2 and 5.

The location of C^{14} in the pyrrolidine ring after feeding labeled acetate, propionate, glycerol or aspartate for varying periods of time was consistent with the hypothesis that these metabolites were converted by way of glycolysis and the tricarboxylic acid cycle to alpha-ketoglutarate, glutamate, and a symmetrical intermediate, ultimately to yield the pyrrolidine ring.

"AUTOXIDATION OF NICOTINE. II. PRODUCTS AND PROPOSED MECHANISM." By F. Paul Gavin and Robert H. Linnell, Department of

Chemistry, University of Vermont, Burlington. *Tobacco Science*, Vol. 6, pages 28-31, February 23, 1962. (T.I.R.C. grantee: Linnell)

Nicotine was vacuum distilled and oxidized by O_2 at $40^\circ C$. The products were studied by paper chromatography, infrared spectroscopy and Karl Fisher titration for water. About 20% of the O_2 appeared as cotinine and another 20% as oxynicotine, whereas 30% appeared as water. An unstable hydroperoxide is proposed. This could split out water to form cotinine, H_2O_2 to form an unstable diradical (which could then react further to form higher molecular weight tars and account for the balance of the O_2 consumption) and the H_2O_2 would then react with nicotine to form the oxynicotine. The reaction is believed to proceed by a free radical mechanism.

"RESIDUAL ARSENIC IN SOILS AND CONCENTRATION IN TOBACCO." By H. G. Small, Jr. and C. B. McCants, Department of Soil Science, North Carolina Agricultural Experiment Station, North Carolina State College, Raleigh. *Tobacco Science*, Volume 6, pages 34-36, March 9, 1962. (T.I.R.C. grantee: McCants)

Arsenicals were removed in 1952 from the list of recommended insecticides for control of hornworms on tobacco and considerable evidence indicates that since that time there has been a sharp decrease in the arsenic content of cigarettes. The objectives of this study were to evaluate the absorption of arsenic by tobacco and to obtain an estimate of the residual levels of arsenic in representative soils used for tobacco production in North Carolina. The survey included all of the major tobacco producing areas in the state.

Arsenic in soil was found to range from 1 to 5 parts per million, with an average for all areas of 2.8 parts per million. This value is close to the 4 parts per million reported by Greaves, J. E. (*Bio. Chem. Bull.* 2:8:519-523; 1913) for a virgin soil and thus suggests no measurable increase from the previous use of arsenicals in the arsenic content of soils used for tobacco.

The arsenic concentration found in the cured leaf in tobacco grown on these soils is from 0.5 to 3.5 parts per million. The average for all leaf samples is 1.5 parts per million.

"INFLUENCE OF ARSENIC APPLIED TO THE GROWTH MEDIA ON THE ARSENIC CONTENT OF FLUE-CURED TOBACCO." By H. G. Small, Jr. and C. B. McCants. *Agronomy Journal*, Volume 54, pages 129-133, March-April 1962.

Field and greenhouse experiments were conducted to study the absorption of arsenic by flue-cured tobacco. The field treatments consisted of a check and rates of lead arsenate (17% As) equivalent to 3, 6, 12, 24 and 48 pounds of arsenic per acre applied to three different soil types in the spring of 1957. Experiments were conducted on the same sites in 1958 and 1959, but no additional As was applied. In the greenhouse, tobacco was grown in sand cultures to which was added a nutrient solution containing various concentrations of soluble As as a sodium arsenate.

Data from the field experiments show that the concentration of arsenic in the cured tobacco varied from 2 parts per million where none was applied to the soil to a maximum of 14.3 parts per million at the 48-pound rate.

There was considerable variation in the arsenic content of the leaves between years and locations. In general, the concentration was highest in those leaves grown in the sandier soil and decreased as the clay and iron content of the soil increased. Phosphorus fertilization also affected the level of As in the leaf, the content being higher where fertilizer phosphorus was applied than where it was omitted.

The arsenic content of the aerial portion of plants grown in the greenhouse was considerably lower than that of the roots, suggesting that the low levels of As in leaves from field grown plants may be due in part to the lack of appreciable translocation.

"DEMETHYLATION IN THE METABOLISM OF (-)-NICOTINE." By Herbert McKennis, Jr., Lennox B. Turnbull, Sorell L. Schwartz, Einosuke Tamaki and Edward R. Bowman, Department of Pharmacology, Medical College of Virginia, Richmond. *Journal of Biological Chemistry*, Volume 237, pages 541-546, February 1962. (T.I.R.C. grantee: McKennis)

The metabolism of (-)-nicotine-methyl- C^{14} has been studied in both the rat and the dog. After administration to the former species, 8 to 13% of the radioactivity of the dose appeared as respiratory carbon dioxide. An examination of the metabolism of (-)-nicotine and the intermediate (-)-cotinine in both species leads to the conclusion that the conversion of cotinine to demethylcotinine is involved in the formation of carbon dioxide- C^{14} .

After administration of nicotine-methyl- C^{14} , cotinine and gamma-(3-pyridyl)-beta-oxo-N-methylbutyramide were isolated from the urine of dogs. All of the radioactivity of the latter compound was found in the N-methyl group. As a consequence of this and other considerations, methylamine arising from the hydrolysis of the keto amide *in vivo* may be an intermediate in the formation of the carbon dioxide- C^{14} observed in the studies.

Other grantor: American Tobacco Company.

"STUDIES ON THE METABOLISM OF (-)-COTININE IN THE HUMAN." By Edward R. Bowman and Herbert McKennis, Jr., Department of Pharmacology, Medical College of Virginia, Richmond. *Journal of Pharmacology and Experimental Therapeutics*, Vol. 135, pages 306-311, March 1962.

After the ingestion of (-)-cotinine, the male human excreted (-)-cotinine, hydroxycotinine, and gamma-(3-pyridyl)-beta-oxo-N-methylbutyramide. The two metabolites were isolated from urine and identified by comparison with authentic compounds previously isolated from dog urine. The data indicate areas of similarity between the dog and the human in the metabolism of (-)-cotinine. In contrast, however, no desmethylcotinine was found in the urine of two human subjects after oral administration of (-)-cotinine. Hydroxycotinine has been obtained for the first time in crystalline form.

"STUDIES ON THE RESPIRATORY AND CARDIOVASCULAR EFFECTS OF (-)-COTININE." By Joseph F. Borzelleca, Edward R. Bowman and Herbert McKennis, Jr., Department of Pharmacology, Medical College of Virginia, Richmond. *Journal of Pharmacology and Experimental Therapeutics*, Volume 137, pages 313-318, September, 1962.

An investigation of some aspects of the pharmacological activity of (-)-cotinine, a metabolite of (-)-nicotine, has demonstrated that, in the anesthetized dog, (-)-cotinine lacks the potent pressor activity associated with the parent compound. In addition, it has been shown that (-)-cotinine has a depressor activity which was not abolished by ordinary blocking doses of atropine or diphenhydramine. The presence of depressor activity in the decerebrate and spinal dog is consistent with the suggestion that the effect may be mediated through the ability of (-)-cotinine to produce, directly or indirectly, a vascular muscular relaxation. The quantities of (-)-cotinine employed to produce the observed pharmacological effects were in excess of amounts which would arise *in vivo* from the metabolism of lethal or non-lethal doses of (-)-nicotine.

"THE CORRECTED STRUCTURE OF A KETOAMIDE ARISING FROM THE METABOLISM OF (-)-NICOTINE." By Herbert McKennis, Jr., Lennox B. Turnbull, Edward R. Bowman and Sorell L. Schwartz, Department of Pharmacology, Medical College of Virginia, Richmond. *Journal of the American Chemical Society*, Vol. 84, pages 4598-4599, Dec. 5, 1962.

The corrected structure of a ketoamide isolated from the urine of dogs and later of rats during the course of studies on the metabolism of (-)-nicotine was established as the methylamide of gamma-(3-pyridyl)-gamma-oxobutyric acid. This evidence, together with the synthesis of the ketoamide, provides opportunities for additional studies on the intermediary metabolism of (-)-nicotine.

Other grantor: American Tobacco Company

VI. Pharmacology

"MECHANISM OF THE POSITIVE CHRONOTROPIC RESPONSE TO NICOTINE." By Floyd E. Leaders and J. P. Long, Department of Pharmacology, University of Iowa College of Medicine, Iowa City. *Journal of Pharmacology and Experimental Therapeutics*, Volume 137, pages 206-212, August 1962. (T.I.R.C. grantee: Long)

The mechanism of the positive chronotropic response to nicotine was studied, using isolated cat atria preparations with parasympathetic (vagus) and sympathetic (poststellate ganglion) nerves intact. The effects of ganglionectomy and reserpinization on the response to nicotine were observed.

Inhibition of the parasympathetic nervous system with hemicholinium (HC-3) abolished both the positive and negative chronotropic responses to nicotine. Both of these responses could again be observed after repeated washing over a 1 to 3 hour period. HC-3 did not inhibit the response to sympathetic nerve stimulation nor did it block the response to nicotine administration when the vagi were not stimulated.

Ganglionectomy followed by nerve degeneration or reserpine administered for 2 days abolished the positive chronotropic response to nicotine. Further, it was demonstrated that there was no evidence of norepinephrine uptake by the atria after ganglionectomy and nerve degeneration. However, norepinephrine uptake was suggested in atria from control animals and those pretreated with reserpine.

The involvement of the parasympathetic nervous system in both the negative and positive phases of the atrial response to nicotine obviates the necessity of postulating sympathetic ganglia in the heart to explain these actions of nicotine. The ability of the parasympathetic nervous system to influence sympathetic nervous system activity has been demonstrated.

Other grantor: U. S. Public Health Service.

VII. Other Studies

"SKIN GRAFTING IN MONGREL DOGS." By David B. Pilcher, M.D., Warren E. Johnson, A.B., Roy Korson, M.D. and Julius H. Jacobson II, M.D., Departments of Surgery and Pathology, University of Vermont College of Medicine, Burlington. *Plastic and Reconstructive Surgery*, Volume 28, pages 670-680, December 1961. (T.I.R.C. grantee: Jacobson)

Preparatory to the study of lung homotransplantation in dogs, the experimental animal of widest choice, it was necessary to obtain data on a feasible technique of skin grafting and reactions of skin autografts and homografts in these animals as a baseline for further transplantation investigations.

Multiple circles 3 cm. in diameter were excised from the shaved back and chest wall of mongrel dogs in areas relatively inaccessible to biting and scratching. Discs of skin from donor animals (homografts) were grafted into six prepared sites, and an autograft into a seventh site, as a control, and four to six discs of skin were interchanged on the same animal (autografts).

On gross examination the homografts and autografts were indistinguishable at 8 days, and by 12 days beginning degeneration was apparent in the homografts. Median survival time of the latter was 16 days.

All homografts were sloughed by 24 days. In addition to a description of the steps involved in healing or rejection, the microscopic analysis sought to answer three questions: (1) Can one tell an autograft from a homograft? (2) Can one tell infection from homograft rejection? (3) Can one distinguish viable from non-viable graft? The answer is a qualified yes in all cases. Viability is easily determined by persistence and regeneration of epidermis and skin appendages.

"FLYING-SPOT INTERFERENCE TELEVISION MICROSCOPE." By P. O'B. Montgomery and L. L. Hundley, Department of Pathology, University of Texas, Southwestern Medical School, Dallas. *Nature*, December 16, 1961, pages 1059-1060. (T.I.R.C. grantee: Montgomery)

The authors developed in their laboratory an all-electronic flying-spot interference television microscope for the rapid determination of cellular dry mass. The system devised has several advantages over previously described techniques: (1) The data on dry mass of whole cells or segments of cells are obtained and recorded by two methods every 10 seconds. (2) The dry-mass images of the specimen are continuously displayed on the monitor tube during the course of the experiments. (3) The visual presentation of the dry-mass image makes positioning of the brightened area of the raster quite easy, and this permits continuous determination of the dry mass of selected areas of the cell.

Other grantors: Atomic Energy Commission, Southwestern Medical Foundation, and Damon Runyon Memorial Fund.

"AN ULTRAVIOLET MICROBEAM TELEVISION SYSTEM." By W. A. Bonner, University of Texas Southwestern Medical School, Dallas, Texas. *Annals of the New York Academy of Sciences*, Volume 97, pages 408-411, June 5, 1962. (T.I.R.C. grantee: P. O'B. Montgomery)

"SIMULTANEOUS ULTRAVIOLET AND VISIBLE LIGHT FLYING SPOT TELEVISION MICROSCOPY." By P. O'B. Montgomery, University of Texas Southwestern Medical School, Dallas, Texas. *Annals of the New York Academy of Sciences*, Volume 97, pages 491-497, June 5, 1962.

These papers describe a versatile television system in which an UV emitting scanner tube replaces the source and primary aperture of conventional UV microbeam systems, and methods of obtaining simultaneous illumination of cellular specimens by different wave lengths of light, which presents distinct advantages in biological study. In order to view a specimen simultaneously in two wave lengths of light two scanner tubes are employed, one emitting UV light and the other visible light.

Other grantors: Atomic Energy Commission, Damon Runyon Memorial Fund for Cancer Research, and the Southwestern Medical Foundation.

"PERIODIC FEVER, AN ENTITY. A COLLECTION OF 52 CASES." By Hobart A. Reimann, M.D., Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa. *American Journal of the Medical Sciences*, Volume 243, pages 162-174, February 1962.

Periodic fever was proposed as an entity separate from other periodic disorders in 1948 and further substantiated by the description of 52 cases in this essay. Periodic fever is characterized by repetitive febrile episodes and autonomic nervous disturbances in predictable cycles of days, weeks or months, or irregularly, in otherwise healthy persons. It also may occur in patients with malignant or other chronic disease.

It is hereditary, begins at any time of life, may last for decades, and may have long spontaneous remissions and may cease. About 10% of victims died, usually in a shock-like state. There is no satisfactory treatment and the cause is unknown. Tobacco played no role in any of the victims who used it. The disorders occasionally appear in families with other neurotic tendencies or migraine. This together with evidence of cerebral dysrhythmia and abnormal neurovascular responses suggests the site of origin to be in the brain.

"HEREDITARY PERIODIC EDEMA. THE INTERRELATION OF FAMILIAL PERIODIC DISORDERS." By Hobart A. Reimann, M.D., Professor of Medicine and Preventive Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa. *American Journal of the Medical Sciences*, Volume 243, pages 727-739, June 1962.

A number of features suggest an interrelation between periodic edema and six or more other periodic entities discussed in this review: Each may be transmitted genetically, has similar periodicity in cycles of days, weeks, or months, vascular disturbances, overlapping features, good health between

episodes, long duration with temporary or permanent remission, and similar histopathologic and electroencephalographic changes.

Whether this group of conditions are unified on the basis of a common underlying provocative rhythm or are regulated by biologic clocks awaits solution by new investigative methods. If genetic factors are responsible, the chances of preventing or curing periodic disorders by means other than the application of eugenic principles do not seem hopeful.

"THE LOW-FAT DIET FOR PERIODIC PERITONITIS." By Hobart A. Reimann, M.D. *American Journal of Gastroenterology*, Volume 38, pages 85-90, July 1962.

Fourteen patients were given a 20-gram fat-diet; episodes of periodic peritonitis were stopped in four, were milder and farther apart in two, ceased temporarily in three, and were not affected in six. None of the victims who smoked tobacco noted any influence of it in his disorder. Alcohol relieved the symptoms slightly in some.

VIII. Review

"THE ACTIONS OF NICOTINE ON CENTRAL NERVOUS SYSTEM FUNCTIONS." By H. Silvette, E. C. Hoff, P. S. Larson and H. B. Haag (deceased), Departments of Pharmacology and of Neurological Science, Medical College of Virginia, Richmond. *Pharmacological Reviews*, Vol. 14, pages 137-173, March 1962. (T.I.R.C. grantee: Haag)

This is a review of 184 scientific papers and testifies to the many lacunae in knowledge on the neuropharmacological effects of nicotine administered to humans and to animals. The pharmacology or toxicology of tobacco-smoking and pharmacology and toxicology of nicotine are not identical, and often are not even comparable.

Not only does tobacco smoke contain many other ingredients, known and unknown, with distinct pharmacological actions of their own, but the dose of nicotine contained in the smoke is not really ascertainable, though it is often estimated. Since this review is concerned with the neuropharmacology of nicotine, the results of "smoking" experiments are not mentioned, except in special circumstances, and then only if these *seem* to be equivalent to results obtained in controlled, quantitative experiments with nicotine.

An account of "smoking" experiments in general was published in *Tobacco, Experimental and Clinical Studies*, by Larson, Haag & Silvette (Williams & Wilkins Co., 1961), in which most of the data on the neuropharmacology of nicotine to about mid-1959 also appears. The present critical review is designed usefully to fill the gap.

In general, small doses of nicotine have a stimulating action on the central nervous system whereas large doses depress. This review covers spontaneous activity, conditioned reflexes, learning, higher cerebral functions, medullary functions, cerebellar functions and spinal functions.

Recipients of Grants

Following is a list of all recipients of grants approved by the Scientific Advisory Board since initial grants were made in late 1954. It should be noted that some of the projects have been completed.

GRANTEE AND INSTITUTION

PROJECT TITLE

("C" indicates project completed; "P" indicates a report has been published by the grantee)

- | | |
|--|--|
| CLARENCE M. AGRESS, M.D., <i>Chief, Cardiovascular Laboratory, Veterans Administration Center, Los Angeles; Associate Clinical Professor of Medicine, University of California, Los Angeles.</i> | Measurement of the functional status of the human heart by frequency spectrum analysis of its vibrational energy (C—P) |
| ANTHONY A. ALBANESE, Ph.D., <i>Director, Nutrition and Metabolic Research Division, The Winifred Burke Relief Foundation, The Burke Foundation Rehabilitation Center, White Plains, N. Y.</i> | The effect of nicotine on protein and amino acid metabolism in humans |
| E. T. ANGELAKOS, M.D., Ph.D., <i>Associate Professor of Physiology, Boston University School of Medicine, Boston.</i> | Release of catecholamines from the isolated heart |
| D. MURRAY ANGEVINE, M.D., <i>Professor of Pathology, University of Wisconsin Medical School, Madison.</i> | Pathologic—anatomic study of cellular changes in human bronchi (C) |
| STEPHEN M. AYRES, M.D., <i>Director of Research, Department of Pulmonary Physiology, Saint Michaels Hospital, Newark, N. J. (now Director, Cardiopulmonary Laboratory, St. Vincent's Hospital, New York City)</i> | Measurement of alveolar-arterial nitrogen difference by gas chromatography (P) |
| FREDERICK W. BARNES, JR., M.D., Ph.D., <i>Associate Professor of Medicine and Physiological Chemistry, Johns Hopkins University School of Medicine, Baltimore, Md. (now Professor of Medical Science, Brown University, Providence, R. I.)</i> | The role of hyperplasia in tissue response to chronic damage (C—P) |
| RALPH S. BECKER, Ph.D., <i>Associate Professor of Chemistry, University of Houston, Houston, Tex.</i> | An investigation of the spectral and chromatographic characteristics of aromatic hydrocarbons (P) |
| SAMUEL BELLET, M.D., <i>Director, Division of Cardiology, Philadelphia General Hospital.</i> | The effect of nicotine on cardiac irritation in the presence of reserpine, and the effect of nicotine on coronary blood flow of dogs with coronary insufficiency (C—P)
Effects of nicotine on the morphology of coronary arteries and aorta; fibrinolytic effects of nicotine on human and animal plasma; effects of cessation of |

GRANTEE AND INSTITUTION

PROJECT TITLE

HYLAN A. BICKERMAN, M.D., *Associate Clinical Professor of Medicine*, and ALVAN L. BARACH, M.D., *retired Clinical Professor of Medicine*, College of Physicians and Surgeons, Columbia University; Columbia Research Service, Goldwater Memorial Hospital, New York

smoking on serum cholesterol levels of chronic smokers (P)

Non-irritant cigarette smoking with observations on the carbon monoxide concentration of arterial blood and alveolar gas after smoking with inhalation and after non-inhalation smoking

RICHARD J. BING, M.D., *Professor of Medicine and Chairman, Department of Medicine*, Wayne State University College of Medicine, Detroit.

The effect of smoking on the coronary blood flow and certain phases of myocardial metabolism in patients with arteriosclerotic or hypertensive cardiovascular disease (P)

Studies in cellular physiology of heart muscle (P)

Measurement of coronary blood flow by means of radioactivated albumin

The effect of smoking on coronary blood flow in patients with arteriosclerotic heart disease and the effect of nicotine on storage of amines in heart muscle (P)

Measurement of coronary blood flow with a system using coincidence counting; the effect of nicotine and change in heart rate on cardiac metabolism and related subjects (P)

FRED G. BOCK, M.S., Ph.D., *Senior Cancer Research Scientist*, Roswell Park Memorial Institute, Biological Station, Springville, N. Y. (see Moore)

Investigation of the biological effects of cigarette smoke (C—P)

JAMES F. BONNER, Ph.D., *Professor of Biology*, California Institute of Technology, Pasadena, Cal.

Enzymatic study of methylation reactions in plant tissue (C—P)

TOM G. BOWERY, Ph.D., *Pesticide Residue Laboratory, Chemistry Department*, North Carolina State College, Raleigh.

TDE and endrin residues in cigarette smoke (C—P)

JOSEF BROZEK, Ph.D., *Professor and Chairman, Department of Psychology*, Lehigh University, Bethlehem, Pa.

Biological characteristics of men and their smoking habits (C—P)

E. M. BUTT, M.D., *Professor of Pathology*, University of Southern California School of Medicine; *Chief Pathologist*, Los Angeles County Hospital, Los Angeles

Pathologic—anatomic study of cellular changes in human bronchi (C)

Study of trace metal storage of pulmonary and liver tissue by spectrographic and chemical methods (C)

RICHARD U. BYERRUM, Ph.D., *Professor of Chemistry*, Michigan State University, East Lansing

Biosynthesis of the pyridine ring of nicotine (C—P)

GRANTEE AND INSTITUTION**PROJECT TITLE**

SISTER M. EMILY CAHILL, Ph.D.,
Chairman, Chemistry Department,
Regis College, Weston, Mass.

Comparison of analytical methods by determining the percent recovery of arsenic added at known levels to tobacco samples and a broad survey of the amount of arsenic present in tobacco samples from a wide variety of sources

WILLIAM H. CARNES, M.D., *Professor of Pathology,* University of Utah College of Medicine, Salt Lake City.

Pathologic-anatomic studies of cellular changes in human bronchi (C-P)

LEOPOLD CERECEDO, Ph.D., *Professor of Biochemistry and Nutrition,* University of Puerto Rico, School of Medicine, San Juan (formerly Professor of Biochemistry, Fordham University, New York)

A study of early chemical changes in the lungs of tumor-bearing rats and mice (C-P)

WILLIAM G. CLARK, Ph.D., *Clinical Associate Professor of Physiological Chemistry,* University of California Medical Center, Los Angeles.

Effect of nicotine and related substances on amine levels in the nervous system

HANS T. CLARKE, D.Sc., *Professor of Biochemistry,* Columbia University College of Physicians and Surgeons, New York (retired, see Gottschall)

Proteolytic activities of the white blood cells of men and the effect on white blood cell activities of carcinogens, nutrition and other influences (C)

JAY D. COFFMAN, M.D., *Instructor in Medicine,* Massachusetts Memorial Hospitals, Boston.

The effect of tobacco smoking on nutritive skeletal muscle blood flow as determined by the radioisotope disappearance technique (P)

JULIUS H. COMROE, JR., M.D., *Director, Cardiovascular Research Institute,* University of California Medical Center, San Francisco

The effect of smoking upon airway resistance (C-P)
Analysis of case histories on emphysema

DEAN M. CONNORS, M.D., *Associate Director, Department of Laboratory Medicine,* St. Mary's Hospital, Madison, Wis.

A study of the alterations in the human bronchial wall occurring with aging, with particular emphasis on elastic tissue changes and associated changes in the bronchial lumen size

PHILIP COOPER, M.D., *Chief, Surgical Service,* Veterans Administration Hospital, Bronx, N. Y.; *Clinical Professor of Surgery,* Albert Einstein Medical College, Bronx.

A study of the effects of cigarette smoking on levels of gastric acid, pepsin, and uropepsin (C-P)

A study of the effect of extracts of tobacco on cultures of tumor and normal cells. Animal transplants of tumor tissue from tissue cultures (C-P)

Study of combined effect of injected viral agents and environmental factors, including carcinogens and tobacco smoke, on the tracheobronchial tree and pulmonary parenchyma of experimental animals and on tissues in organ culture

GRANTEE AND INSTITUTION

PROJECT TITLE

ALBERT DAMON, M.D., Ph.D., <i>Assistant Professor of Medical Anthropology, Department of Industrial Hygiene, Harvard School of Public Health, Boston.</i>	Body form, smoking, and alcohol consumption among Italian-American men (C—P)
R. F. DAWSON, Ph.D., <i>Professor of Botany, Columbia University, New York.</i>	An investigation of the metabolism of pyridine compounds in the tobacco plant (C—P)
ANDREW S. DIBNER, Ph.D., <i>Executive, Psycho-Research, The Age Center of New England, Inc., Boston, Mass. (see Whiskin).</i>	Psychological and behavioral characteristics of inhalers among smokers (C—P)
EDWARD F. DOMINO, M.D., <i>Associate Professor of Pharmacology, University of Michigan, Ann Arbor.</i>	Effects of tobacco smoke and nicotine on the central nervous system (P)
RALPH L. DOREMAN, Ph.D., <i>Director of Laboratories, Worchester Foundation for Experimental Biology, Shrewsbury, Mass.</i>	Evaluation of tobacco consumption on the basis of nicotine or nicotine metabolites in body fluids and carbon monoxide content of blood
JOHN W. ECKSTEIN, M.D., <i>Assistant Professor of Internal Medicine, College of Medicine, State University of Iowa, Iowa City.</i>	Responses of the peripheral veins in man to the intravenous administration of nicotine (P) Foot blood flow responses to smoking in the presence of hyperlipemia and hypertension
HANSEL FALK, Ph.D., <i>Senior Research Associate, Department of Pathology, University of Southern California School of Medicine, Los Angeles. (now Head, Chemistry Section, Carcinogenesis Studies Branch, National Cancer Institute, Bethesda, Md.)</i>	Examination of cigarette paper and cigarette smoke condensates for aromatic polycyclic hydrocarbons (C) A compilation of fluorescence spectra of polycyclic aromatic hydrocarbons and closely related compounds which are of interest in the study of air pollutants, and cigarette smoke in relation to lung cancer etiology (C—P) The effects of tobacco smoke condensate on the defense mechanisms of the rat in detoxification of polycyclic aromatic hydrocarbons and the competitive inhibition between the polycyclic hydrocarbons in condensate with regard to carcinogenesis (C) The physical and chemical properties of mucus under normal conditions and following exposure to aerosol irritants (C)
DANA L. FARNSWORTH, M.D., <i>Henry K. Oliver Professor of Hygiene and Director of University Health Services, Harvard University, Cambridge, Mass. (see Heath and McArthur).</i>	Personality and smoking in college graduates; a fifteen-year follow-up study (C)

GRANTEE AND INSTITUTION

FRANK C. FERGUSON, JR., M.D.,
Chairman, Department of Pharmacology, Albany (N. Y.) Medical College.

RUSSELL S. FISHER, M.D., *Chief Medical Examiner, State of Maryland; Professor of Legal Medicine, University of Maryland Medical School, Baltimore.*

B. L. FREEDLANDER, M.D., *Director of Cancer Research, Mount Zion Hospital and Medical Center, San Francisco. (deceased, see French)*

FREDERICK A. FRENCH, A.B., *Director of Cancer Chemotherapy Research, Mount Zion Hospital and Medical Center, San Francisco. see (Freeland)*

JACK FREUND, M.D., *Assistant Professor of Pharmacology, Medical College of Virginia, Richmond.*

ARTHUR FURST, Ph.D., *Director, Institute of Chemical Biology, University of San Francisco.*

GEORGE O. GEY, M.D., *Director, Finney-Howell Cancer Research Laboratory; Associate Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.*

THOMAS M. GOCKE, M.D., *Associate Professor of Preventive Medicine and Community Health, Seton Hall College of Medicine and Dentistry, Jersey City, N. J.*

IRA GORE, M.D., *Professor of Pathology, Boston University School of Medicine; Pathologist, Massachusetts Memorial Hospitals, Boston.*

PROJECT TITLE

Effects of tobacco smoke upon the function of the cardiovascular system in animals and man (C)

Pathologic-anatomic study of cellular changes in human bronchi (C)

Experiments on the possible carcinogenic and cocarcinogenic action of tobacco products (C—P)

Carcinogenicity, cocarcinogenicity and anti-carcinogenicity of dietary factors in relation to pulmonary tumors. Possible interrelationship of tobacco bases and dietary factors. Chemical studies on pyridine bases including niacin analogs (C)

Correlation of multitechnical procedures performed on the peripheral circulation of normal individuals in recumbent and erect positions and after exercise before and after sham and actual smoking (C)

A study of the effects of cigarette smoking on the peripheral circulation of individuals with arteriosclerosis obliterans and other peripheral vascular diseases, utilizing multitechnical procedures (C)

A controlled study to evaluate the effect of administration of trace metals (with or without exposure to cigarette smoke) on the incidence of pulmonary adenomas in Strain A mice

Fellowships for studying the culture of human lung tissue and the effects of known and possible carcinogenic agents upon such tissue (C—P)

Characteristics of normal cell growth in culture in relation to invasive carcinoma, especially in the lung

A study of the nasal and pharyngeal bacterial flora of smokers, non-smokers and ex-smokers

Interactions of arterial acid mucopolysaccharides

GRANTEE AND INSTITUTION

GERTRUDE Y. GOTTSCHALL, Ph.D., *Assistant Professor of Biochemistry, Department of Pathology and Microbiology, The Rockefeller Institute for Medical Research, New York. (see Clarke)*

A. CLARK GRIFFIN, Ph.D., *Head of Biochemistry Department, M. D. Anderson Hospital and Tumor Institute, University of Texas Medical Center, Houston.*

MORTON I. GROSSMAN, Ph.D., M.D., *Associate Clinical Professor of Medicine, University of California Medical Center, Los Angeles.*

CARL C. GRUHZIT, Ph.D., M.D., *Associate in Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine, Philadelphia (now Lecturer in Physiology, University of Hong Kong)*

H. B. HAAG, M.D., *Professor of Pharmacology, Medical College of Virginia, Richmond. (deceased, see Larson)*

JOSEPH H. HAFKENSCHIEL, M.D., *Director, Cardiopulmonary Unit, Lankenau Hospital, Philadelphia.*

RICHARD J. HAVEL, M.D., *Assistant Professor of Medicine, University of California Medical School, San Francisco.*

HERBERT R. HAWTHORNE, M.D., *Chairman, Department of Surgery, University of Pennsylvania Graduate School of Medicine, Philadelphia.*

CLARK W. HEATH, M.D., *Professor of Medicine and Director of Health Services, Tufts University, Medford, Mass. (see Farnsworth and McArthur)*

PAULINE HEIZER, Ph.D., *Research Associate in Cytology and Cytochemistry, San Francisco Institute of Medical Sciences, San Francisco. (see Richards)*

PROJECT TITLE

Proteolytic activities of the white blood cells of man and the effect on white blood cell activities of carcinogens, nutrition and other influences (C)

The effect of exposure to cigarette smoke on the induction of cancer by chemical compounds (C—P)

The effect of smoking on certain gastric functions (C)

Pharmacologic study of nicotine and related alkaloids (C)

Preparation for publication of a book on the biologic aspects of tobacco and smoking (C—P)

Measurement of coronary blood flow, cardiac work and cardiac oxygen and carbohydrate metabolism in normotensive subjects before and after intravenous nicotine and after smoking standard cigarettes (C—P)

A study of the effects of smoking and nicotine administration on sympatho-adrenal function and fatty acid metabolism (C)

Attempts to induce pulmonary neoplasms in experimental animals by exposure of the tracheobronchial system to tobacco smoke (C)

Personality and smoking in college graduates: a fifteen-year follow-up study (C—P)

A comparative study of early histological and DNA changes in the epidermis of two strains of mice (C57 Blacks and Swiss Websters) after daily applications of whole cigarette smoke condensate (alone and combined with croton oil) and the carcinogens 20-methylcholanthrene and 3,4-benzpyrene (C)

GRANTEE AND INSTITUTION

PROJECT TITLE

LAWRENCE L. HESTER, JR., M.D., <i>Professor and Chairman, Department of Obstetrics and Gynecology, Medical College of South Carolina, Charleston.</i>	The relationship of the use of tobacco products to the outcome of pregnancy (C)
EBBE CURTIS HOFF, PH.D., M.D., <i>Professor and Chairman, Department of Neurological Science, Medical College of Virginia, Richmond.</i>	Cerebral autonomic changes produced by tobacco smoke, nicotine or cotinine, a metabolite of nicotine
RUSSELL L. HOLMAN, M.D., <i>Professor and Head, Department of Pathology, Louisiana State University School of Medicine, New Orleans. (deceased, see McGill and Strong)</i>	Pathologic-anatomic study of cellular changes in human bronchi (C) The influence of tobacco smoking on acute myocardial infarction (C)
FREDDY HOMBURGER, M.D., <i>President, Bio-Research Institute, Inc., Cambridge, Mass.</i>	Studies on carcinogenesis and the bio-assay of carcinogenic agents (P) Comparative studies of effects of various tobacco smoke condensates on skins of mice (C) Systemic effects of three tobacco smoke condensates (C)
ROBERT W. HULL, PH.D., <i>Associate Professor, Department of Biological Science, Northwestern University, Evanston, Ill.</i>	Photodynamic activation of carcinogenic hydrocarbons: (a) standardization of assay techniques utilizing protozoa; (b) investigation of the mechanisms of activation and response to aromatic carcinogens by protozoa (P)
GEORGE JACOBSON, M.D., <i>Professor and Head of Radiology, University of Southern California School of Medicine, Los Angeles.</i>	The influence of certain environmental factors in the genesis of neoplastic disease in tuberculosis patients and in children
JERRY HART JACOBSON, M.D., <i>Director of Electrophysiology, New York Eye and Ear Infirmary, New York.</i>	A comparison of electroretinography as a means of evaluating the effect of vasoconstrictor drugs upon cerebral and retinal circulation with other techniques for this determination (C)
JULIUS H. JACOBSON II, M.D., <i>Associate Professor of Surgery and Director of Surgical Research, College of Medicine, University of Vermont, Burlington.</i>	Lung homotransplantation (C-P)
MURRAY E. JARVIK, PH.D., <i>Associate Professor of Pharmacology, Albert Einstein College of Medicine, Bronx, N. Y.</i>	Pilot study of habituation to nicotine by means of rhesus monkeys (C)
ANDREW A. KANDUTSCH, PH.D., <i>Staff Scientist, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.</i>	To determine to what extent tobacco 'tar' mimics the action of carcinogenic hydrocarbons in the skin and other tissues (C)

GRANTEE AND INSTITUTION

ARNOLD R. KAPLAN, Ph.D., *Director, Laboratory of Medical Genetics, Cleveland Psychiatric Institute and Hospital.*

ELIHU KATZ, Ph.D., *Associate Professor of Sociology, University of Chicago.*

ANGEL KEYS, Ph.D., *Professor of Physiological Hygiene and Director, Laboratory of Physiological Hygiene, University of Minnesota School of Public Health, Minneapolis.*

JOSEPH B. KIRSNER, M.D., *Professor of Medicine, University of Chicago School of Medicine.*

KENNETH P. KNUDTSON, M.D., *Assistant Chief, Laboratory Service, Veterans Administration Hospital, Seattle, Wash.; Professor of Pathology, University of Washington Medical School, Seattle.*

ALVIN I. KOSAK, Ph.D., *Associate Professor of Chemistry, Washington Square College, New York University, New York.*

ROBERT A. KUHN, M.D., *All Souls Hospital, Morristown, N. J.*

MARVIN KUSCHNER, M.D., *Professor of Pathology, New York University College of Medicine; Director of Pathology, Bellevue Hospital, New York.*

CHARLES W. LA BELLE, Ph.D., *Assistant Professor of Environmental Hygiene, Department of Preventive Medicine, Jefferson Medical College, Philadelphia.*

THOMAS C. LAIPPLY, M.D., *Professor of Pathology, Northwestern University Medical School; Chairman, Department of Pathology, Wesley Memorial Hospital, Chicago.*

PAUL S. LARSON, Ph.D., *Professor of Pharmacology, Medical College of Virginia, Richmond. (see McKennis).*

PROJECT TITLE

Examination of the extent of, and constitutional basis for, correlations between the following: (1) taste thresholds for quinine and 6-N-propylthiouracil, (2) constitutional predisposition to pathologic variables, (3) individual differences in smoking practices, and (4) food dislikes

Social and psychological constraints on the translation of motives into action: The case of cigarette smoking

Characteristics of men, including smoking, in populations differing in the incidence of coronary heart disease (C—P)

The effect of tobacco smoking upon basal gastric secretions in man (C)

Pathologic—anatomic study of cellular changes in human bronchi (C—P)

The isolation and identification of certain lower-boiling components of cigarette smoke (C—P)

Possible effects of tobacco upon cerebral circulation (P)

Pathologic—anatomic study of cellular changes in human bronchi (C)

Effect of cigarette smoke on pulmonary clearance

Pathologic—anatomic study of cellular changes in human bronchi (C)

Classification, prognosis and etiologic factors of primary tumors of the lung

Preparation for publication of a book on the biologic aspects of tobacco and smoking (C—P)

Enzymatic transformations of nicotine and related compounds (P)

The possible effect of tobacco smoke and nicotine on ascorbic acid metabolism (C)

GRANTEE AND INSTITUTION

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CHARLES C. MCARTHUR, Ph.D., *Psychologist to the University Health Services*, Harvard University, Cambridge, Mass. (see Heath and Farnsworth)

PROJECT TITLE

Studies in bronchitis: a correlated investigation of (a) the effect of smoking on the bacteriology of the respiratory tract of humans, and (b) the effect of cigarette smoke and sulfur dioxide (air pollutant) on the clearing of bacteria from the respiratory tracts of small animals (mice, rats) (P)

A correlated histological, cytological and cytochemical study of the tracheo-bronchial tree of mice exposed to cigarette smoke (C—P)

The interrelation between influenza virus infections, exposure to cigarette smoke and other factors in the development of pulmonary and bronchial lesions in mice

Measurement of the differential blood flow in the mammalian lung during the acute period of smoke inhalation, using the open chest animal and the method and principle of gamma emitting radioactive graded microspheres

The oxidation of nicotine by gaseous oxygen: mechanism, products and kinetics. (C—P)

The autoxidation of nicotine (P)

Epidemiological factors in lung cancer

Cardiovascular effects of nicotine (P)

Environmental factors and pulmonary disease. I. Asbestos dust

Effect of tobacco smoke and tobacco residues on methylcholanthrene-induced skin carcinogenesis in mice (C)

Possible interactions of viruses and substances in tobacco smoke condensate (C—P)

Social and personal determinants of smoking behavior (C—P)

The social mediation of smoking behavior (C)

GRANTEE AND INSTITUTION

CHARLES B. McCANTS, Ph.D., *Associate Professor of Soils*, School of Agriculture, North Carolina State College, Raleigh.

HENRY C. McGILL, JR., M.D., *Acting Head, Department of Pathology*, Louisiana State University School of Medicine New Orleans. (see Holman and Strong)

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VICTOR A. McKUSICK, M.D., *Professor of Medicine*, Johns Hopkins University School of Medicine, Baltimore, Md.

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GEORGE H. MOORE, Ph.D., M.D., *Director*, Roswell Park Memorial Institute, Buffalo, N. Y. (see Bock)

HURLEY LEE MOTLEY, M.D., *Professor of Medicine and Director, Cardio-Respiratory Laboratory*, University of Southern California School of Medicine, Los Angeles.

PROJECT TITLE

Arsenic content of soils and absorption by the tobacco plant (C—P)

The effects of environmental factors on development of atherosclerosis as revealed by autopsy of accident victims

Study of lung function in smokers and nonsmokers (C—P)

Enzymatic transformations of nicotine and related compounds (P)

A combined genetic, physiologic, clinical and epidemiologic study of Buerger's disease (C—P)

A study of Buerger's disease among the Jewish ethnic groups in Israel

The behavioral effects of smoking under stress (C)

Influence of tobacco smoking on the blood flow of skin and of muscles of extremities in sympathectomized and unsympathectomized subjects (C)

Influence of nicotine (i.v.) and tobacco smoking on blood flow in human skin and skeletal muscle (C—P)

Investigation of the role of the nucleolus in the normal and the malignant cell (P)

An investigation of the physiological effects of direct inhalation of tobacco smoke by laboratory animals and the study of the biological response of laboratory animals to continuous ingestion of diet-tobacco product mixtures (C)

A study of the effects of smoking on pulmonary function (C—P)

GRANTEE AND INSTITUTION

WILLIAM S. MURRAY, Sc.D., *Research Associate*, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Me.

DONALD M. PACE, Ph.D., *Professor of Physiology and Director, Institute for Cellular Research*, University of Nebraska, Lincoln.

EDWARD W. PELIKAN, M.D., *Chairman and Professor of Pharmacology and Experimental Therapeutics*, Boston University School of Medicine, Boston.

OTAKAR J. POLLAK, M.D., Ph.D., *Executive Director*, Dover Medical Research Center, Inc., Dover, Del.

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C. M. POMERAT, Ph.D., *Director of Biological Research*, Pasadena Foundation for Medical Research, Pasadena, Cal.

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WALTER REDISCH, M.D., New York University Research Service, Goldwater Memorial Hospital, Welfare Island, New York. (see Sulzberger)

HOBART A. REIMANN, M.D., *Professor of Medicine*, Hahnemann Medical College and Hospital, Philadelphia.

PROJECT TITLE

The production of genetically controlled animals and tumors for use in experimental research on tobacco in relation to health (C)

Studies of the mammary tumor-promoting qualities of a virus-like principle, under varying hormonal and aging conditions (C)

Fellowship for training in tissue culture techniques (C)

Study of the effects of tobacco smoke constituents on various strains of tissue cells cultivated *in vitro* (P)

A study of structure-activity relationships among drugs which affect nicotine-sensitive physiological mechanisms (P)

Possible effect of tobacco derivatives on arterial and myocardial tissue cultures (C-P)

Chemical and viral carcinogenesis in the axenic ("germfree") animal

Fellowships for studying the culture of human lung tissue and the effects of known and possible carcinogenic agents upon such tissue (C-P)

Pathologic-anatomic study of cellular changes in human bronchi (C-P)

Application of a new bioassay technique in examination of cigarette smoke condensates for possible carcinogens (C-P)

Carcinogenesis in the laboratory animal: a comparison of species response to standardized sites of application.

A comparative study of the effects of 3-methylcholanthrene and cigarette smoke condensate applied to the oral tissues of Swiss mice (ICR) conditioned with alcohol and/or carbon tetrachloride

Vascular responses to tobacco smoking in patients with vascular disease

The possible effect of tobacco or nicotine in periodic disorders, a newly-recognized syndrome (C-P)

GRANTEE AND INSTITUTION

VICTOR RICHARDS, M.D., *Professor of Surgery and Executive Head, Department of Surgery, Stanford University School of Medicine, San Francisco.* (see Heizer)

R. H. RIGDON, M.D., *Professor of Pathology and Director, Laboratory of Experimental Pathology, University of Texas Medical Branch, Galveston.*

SYDNEY C. RITTENBERG, Ph.D., *Professor of Bacteriology, University of Southern California, Los Angeles.*

BENSON B. ROE, M.D., *Associate Professor of Surgery, Department of Surgery, University of California School of Medicine, San Francisco.*

BENJAMIN A. RUBIN, Ph.D., *Assistant Professor of Public Health and Preventive Medicine, Baylor University College of Medicine, Houston, Texas.* (now Manager, Biological Products Development, Wyeth Laboratories, Philadelphia)

HENRY I. RUSSEK, M.D., *Consultant in Cardiovascular Disease, U. S. Public Health Service Hospital, and President, The Russek Foundation, Inc., Staten Island, N. Y.*

WILLIAM O. RUSSELL, M.D., *Pathologist-in-chief, M.D. Anderson Hospital and Tumor Institute, University of Texas Medical Center, Houston.*

PETER F. SALISBURY, M.D., *Head, Intensive Treatment Center, Saint Joseph Hospital, Burbank, Cal.*

PAUL D. SALTMAN, Ph.D., *Assistant Professor of Biochemistry, University of Southern California School of Medicine, Los Angeles.*

ALVIN R. SCHMIDT, Ph.D., *Director of Counseling, Tufts University, Medford, Mass.*

PROJECT TITLE

A comparative study of the effects of whole and fractional extracts of cigarette smoke and those of known carcinogens on (1) the cytology and nuclear DNA content of epidermis in various strains of mice and/or (2) the cytology and nuclear DNA content of lung and epithelium of the bronchial tree of mice and hamsters (C)

Effects of tobacco smoke condensate on the respiratory tract and other tissues of the duck (C—P)

The bacterial degradation of nicotine and related compounds. The objective of the project is the elucidation of the intermediary metabolism of nicotine oxidation (C—P)

Study of the action of negatively charged ions on tracheobronchial ciliary action in the human patient (C)

An evaluation of the phenomenon of tumor growth enhancement as an assay for carcinogens among the polycyclic hydrocarbons and related compounds (C)

Emotional stress (occupational), tobacco consumption and coronary heart disease

Pathologic—anatomic study of cellular changes in human bronchi (C)

Influence of nicotine and catecholamines upon coronary vasomotor tonus in normal and atherosclerotic dogs (P)

The enzymatic mechanism for the dark fixation of CO₂ by tobacco (C—P)
Some aspects of amino acid metabolism in tobacco leaves (C—P)

Study of attitudes toward, as well as extent, type and history of, tobacco smoking in a young college population. Study of some of the relationships of smoking and nonsmoking to family history, type of secondary schooling, academic interests, academic achievement, and, social relationships characteristics (C)

GRANTEE AND INSTITUTION

ISAAC SCHOUR, D.D.S., Ph.D., D.Sc.,
*Professor of Histology and Embryology
and Dean, University of Illinois Col-
lege of Dentistry, Chicago.*

MAURICE S. SEGAL, M.D., *Clinical
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sity School of Medicine, Boston, Mass.;
Director, Department of Inhalation
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CARL C. SELTZER, Ph.D., *Research
Fellow in Physical Anthropology, Har-
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Department of Nutrition, Harvard
School of Public Health, Boston.*

CHARLES E. SHERWOOD, M.D., *As-
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DAVID L. SIMON, M.D., *Instructor in
Medicine and Fellow in Cardiovascu-
lar Research, University of Cincinnati
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oratory, Cincinnati General Hospital.*

LOUIS A. SOLOFF, M.D., *Professor of
Clinical Medicine and Chief, Division
of Cardiology, Temple University Med-
ical Center, Philadelphia.*

ERNEST SONDHEIMER, Ph.D., *Asso-
ciate Professor of Biochemistry, State
University College of Forestry at Syra-
cuse University, Syracuse, N. Y.*

T. M. SONNEBORN, Ph.D., *Distin-
guished Service Professor of Zoology,
Indiana University, Bloomington.*

SAM SOROF, Ph.D., *Research Associate,
The Institute for Cancer Research and
Lankenau Hospital Research Institute,
Philadelphia.*

FREDERICK J. STARE, Ph.D., *Profes-
sor of Nutrition, Harvard School of
Public Health, Boston.*

PROJECT TITLE

Histologic changes in the oral, pharyn-
geal and nasal tissues of experimental
animals subjected to tobacco smoke
(C—P)

Effects of cigarette smoking on lung func-
tion in normal subjects and patients
with certain respiratory disease condi-
tions (C—P)

Relationship of cigarette smoking to
chronic (obstructive) pulmonary em-
physema (C)

Morphology and smoking in college
graduates: a fifteen-year follow-up
study (P)

Harvard-Johns Hopkins study of body
form as related to smoking, and the
precursors of hypertension and cor-
onary artery disease.

Investigation into the natural history of
carcinoma of the lung with particular
reference to the radiographic appear-
ance of such processes, the earliest
manifestation of cancer on chest X-
ray photographs and the tabulation of
the relationship of smoking habits and
occupation with the incidence of lung
cancer (C—P)

The effects of chewing tobacco on the
cardiovascular system of man (C—P)

The effects of pipe smoking and cigar
smoking on the cardiovascular system
of man (C—P)

Study of effect of tobacco smoking on
surfactant and on specific fatty acids

The purification and structure determina-
tion of the chlorogenic acid isomers

Checking and extending the Stephano
Paramecium test for carcinogenicity
(C)

Chemical and physical studies of the
tissue proteins involved in chemical
carcinogenesis (C—P)

Experimental studies of cancer utilizing
a new technique to see if various
'tars' extracted from tobacco may in-
cite the formation of lung tumors (C)

GRANTEE AND INSTITUTION

PROJECT TITLE

C. HAROLD STEFFEE, M.D., *Director of Laboratories, Methodist Hospital, Memphis, Tenn.*

Studies of carcinogenesis in mice

JACK P. STRONG, M.D., *Associate Professor of Pathology, Louisiana State University School of Medicine, New Orleans. (see Holman and McGill)*

The effects of environmental factors on development of atherosclerosis as revealed by autopsy of accident victims

MARION B. SULZBERGER, M.D., *Professor and Chairman, Department of Dermatology and Syphilology, New York University-Bellevue Medical Center, New York. (retired, see Redisch)*

Investigation of the effects of tobacco on the human vascular system, based on the fact that certain tobacco effects are due to allergic susceptibility of specific individuals rather than to obligatorily toxic products in tobacco smoke, and that patients with occlusive vascular diseases respond differently than healthy smokers (P)

RENATO TAGIURI, Ph.D., *Associate Professor of Psychology, Graduate School of Business Administration, Harvard University, Boston.*

Critical review of literature on psychology of smoking

CAROLINE BEDELL THOMAS, M.D., *Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.*

The significance of different individual patterns of circulatory response to cigarette smoking (C—P)
Studies of genetic differences between smokers and nonsmokers (C—P)
Studies of psychological differences between smokers and nonsmokers as shown by comparison of figure drawings (C—P)

TISSUE CULTURE ASSOCIATION

To assist in establishing of summer training course in tissue culture techniques at University of Colorado Medical School, Denver, Colo. (C)

JAMES E. P. TOMAN, Ph.D., *Associate Professor of Physiology and Pharmacology, Chicago Medical School.*

Mechanisms of the psychotropic effects of nicotine

JANET TRAVELL, M.D., *Associate Professor of Clinical Pharmacology, Cornell University Medical College, New York.*

Effects of nicotine in the rabbit with experimental coronary atherosclerosis (C—P)

E. D. WARNER, M.D., *Professor of Pathology, State University of Iowa College of Medicine, Iowa City.*

Pathologic-anatomic study of cellular changes in human bronchi (C—P)
Correlation of bronchial epithelial changes with comparable changes in other organs—a pathologic-anatomic study (C—P)

SHIELDS WARREN, M.D., *Director of Laboratories, Cancer Research Institute, New England Deaconess Hospital, Boston.*

The pattern of metastasis of carcinoma of the lung in man (C)
Histopathology of human lung cancer

CONTINUED

GRANTEE AND INSTITUTION

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RUSSELL W. WELLER, M.D., *Pathologist*, Memorial Hospital of Chester County, West Chester, Pa.; *Associate Professor of Pathology*, Hahnemann Medical College, Philadelphia.

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JOHN P. WYATT, M.D., *Professor of Pathology*, St. Louis University School of Medicine, St. Louis, Mo.

PROJECT TITLE

Effect of cigarette smoking on cerebral blood flow, cerebral metabolism, blood gases, blood pH, arterial pulse pressure curves, electrocardiograms, and electroencephalograms (C)

Pathologic-anatomic study of cellular changes in human bronchi (C)
A selected, extended and detailed study of human bronchial mucosa

A qualitative and quantitative study of the individual polyphenol content of cigarette tobacco and the smoke and 'tars' resulting from cigarette smoking and also study of the fate of these compounds in the animal respiratory system (C-P)

The identification of individual polyphenolic compounds present in the smoke from cigarettes and the preparation, where feasible, of these compounds for studies on their metabolism and possible effect on human health.

The determination of the chronic effects of orally administered nicotine on serum cholesterol and phospholipids; the electrocardiographic response to ergonovine; and the vascular pathology of cholesterol-fed rabbits (C-P)

A study of central actions of nicotine

Pilot study of smoking habits of Age Center members (C-P)

An investigation of biochemical factors associated with susceptibility to lung cancer

The effect of prolonged inhalation of tobacco smoke and of prolonged abstinence from the use of tobacco on the peripheral vascular response to acute inhalation of tobacco smoke in man (C-P)

Evaluation of etiologic factors, such as occupational hazards and habits, anatomic peculiarities in the long-term survival of patients following resection for bronchogenic carcinoma

An investigation into the nature of the pigmentary lesions in centrilobular emphysema (C)